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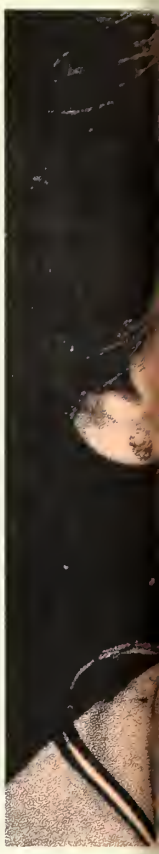

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In an original study designed to evaluate hypnotic effectiveness for 28 consecutive nights of use, the relative ineffectiveness of pentobarbital was established after only two weeks.[3] Dalmane, however, remained effective not only for 14 nights, but for 28 nights in chronic insomniacs,[3,4] without increasing dosage from night to night. Prolonged administration of Dalmane is seldom necessary, but when it is, periodic blood counts and liver and kidney function tests should be performed.

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Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

***Usage in Pregnancy:* Several studies of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) suggest increased risk of congenital malformations during the first trimester of pregnancy. Dalmane, a benzodiazepine, has not been studied adequately to determine whether it may be associated with such an increased risk. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, limit initial dosage to 15 mg to preclude oversedation, dizziness and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

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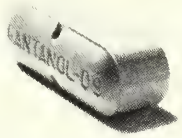

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Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimethamine in congenital toxoplasmosis). *Usual adult dosage:* 2 Gm (2 DS tabs or 4 tabs or 4 teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection.

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References:

1. Dornfeld L, Kane R. Metolazone in essential hypertension. The long-term clinical efficacy of a new diuretic. *Curr Ther Res* **18**: 527-533, 1975
2. Data on file, Medical Department, Pennwalt Prescription Products

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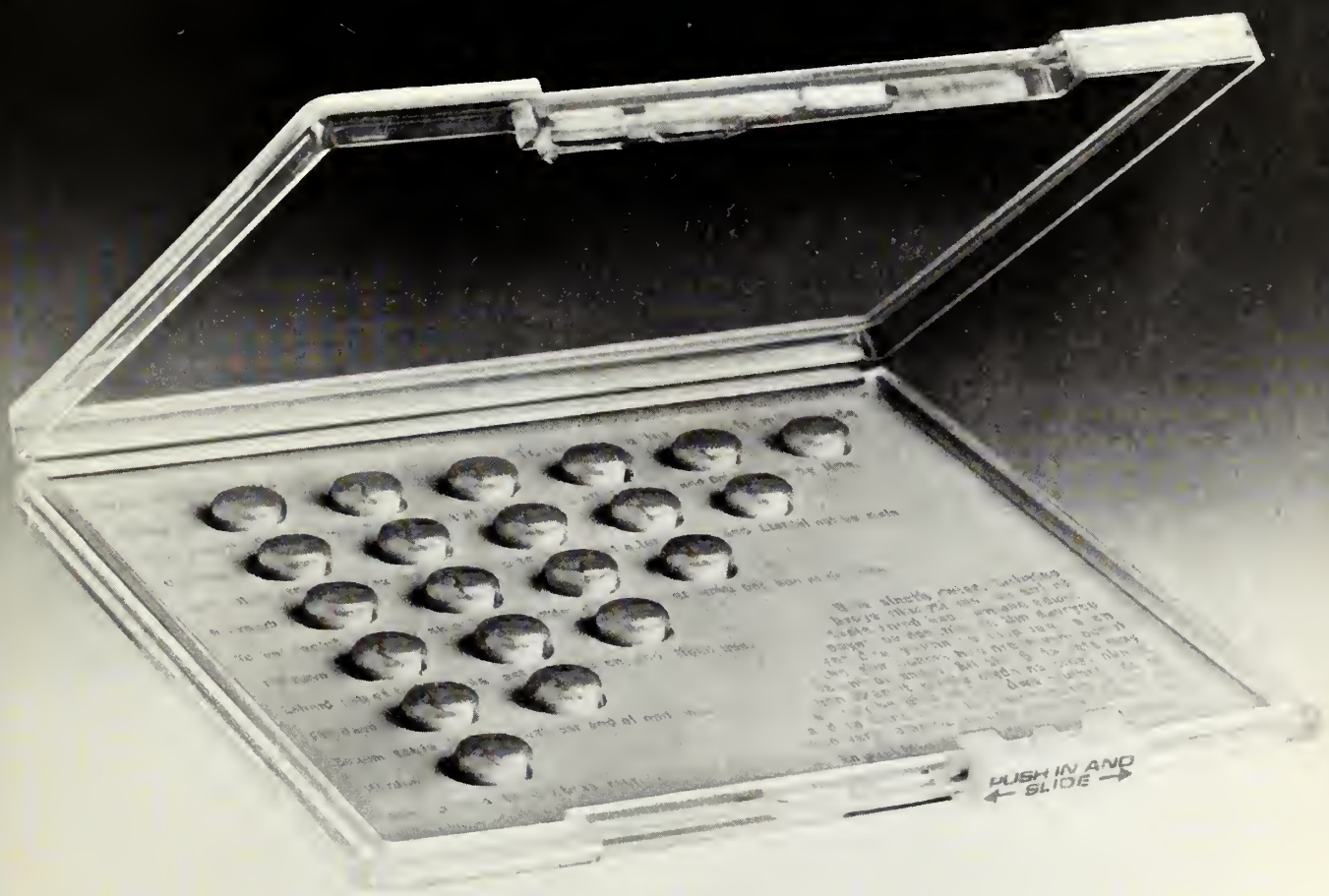

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

EMERGENCIES IN MEDICAL PRACTICE—Tenth Edition—Edited by C. Allan Birch, MD, FRCP, Honorary Consulting Physician, Chase Farm Hospital, Enfield, Middlesex. Churchill Livingstone - Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 864 pages, $38.00.

EPIDEMIOLOGY AND COMMUNITY HEALTH IN WARM CLIMATE COUNTRIES—The late Robert Cruickshank, CBE, MD, FRCP, FRCPE, DPH, FRSE, Hon LLD(Aberd), Formerly, Professor of Bacteriology, University of Edinburgh; Professor of Social and Preventive Medicine, University of the West Indies, Kingston; Kenneth L. Standard, MB, BS(Lond-UCWI), MD(Lond), FFCM, MPH, FRSH, FAPHA, Professor of Social and Preventive Medicine, University of the West Indies; Hugh B.L. Russell, MRCS, LRCP, MFCM, DTM&H, DPH, Senior Lecturer, Department of Community Medicine, University of Edinburgh; Formerly, WHO Regional Public Health Officer, Eastern Mediterranean; Regional Adviser on Community Development, Southeast Asia, and WHO Liaison Officer with the Economic Commission for Africa; Foreword by Professor E.K. Cruickshank, OBE, MD, FRCP, FACP(Hon), Dean of Postgraduate Medicine, University of Glasgow. Churchill Livingstone - Medical Division, Longman Inc , 19 West 44th Street, New York City (10036), 1976. 492 pages, $18.50 (paper), $32.00 (cloth).

ETHICS OF NEWBORN INTENSIVE CARE—Edited by Albert R. Jonsen, PhD, Associate Professor of Bioethics; and Michael J. Garland, PhD, Lecturer in Bioethics, University of California, San Francisco School of Medicine. A Joint Publication of Health Policy Program, School of Medicine, University of California, San Francisco, and Institute of Governmental Studies, University of California, Berkeley, 1976. Send order to the Institute of Governmental Studies, 109 Moses Hall, University of California, Berkeley, CA 94720. Single copies are free on request. 193 pages, $4.00 for additional copies (paperback).

FAIRBANK'S ATLAS OF GENERAL AFFECTIONS OF THE SKELETON—Second Edition—Ruth Wynne-Davies, MB, BS(Lond), PhD(Edin), FRCS, Reader, Department of Orthopaedic Surgery (Genetics Research), University of Edinburgh; Honorary Consultant Orthopaedic Surgeon, the Lothian Health Board, Edinburgh; and T.J. Fairbank, MA, MB, BChir (Camb), FRCS, Senior Consultant Orthopaedic Surgeon, Cambridgeshire Area Health Authority (T), East Anglian Regional Health Authority. Churchill Livingstone - Medical Division, Longman, Inc., 19 West 44th Street, New York City (10036), 1976. 262 pages, $49.50.

A GUIDE TO HEALTH FACILITIES—Personnel and Management—Second Edition—Robert M. Sloane, MS, FACHA, Medical Center Administrator, City of Hope National Medical Center, Duarte, California; and Beverly LeBov Sloane, MA; with 65 illustrations prepared by Kurt Smolen. The C. V. Mosby Company, 3301 Washington Boulevard, St. Louis (63103), 1977. 209 pages, $6.95 (softbound).

HORMONE ASSAYS AND THEIR CLINICAL APPLICATION—Fourth Edition—Edited by John A. Loraine, DSc, MB, PhD, FRCP(Ed), Member of MRC External Scientific Staff, Department of Community Medicine, University of Edinburgh; and E. Trevor Bell, BSc, PhD, Research and Development Director, Unisabi, SA, St Denis de l'Hotel, France. Churchhill Livingstone - Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 692 pages, $38.50

(Continued on Page 14)

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Indications:

Streptococcus pyogenes (Group A beta hemolytic streptococcus)—Upper and lower respiratory tract infections, skin, and soft tissue infections of mild to moderate severity, where oral medication is preferred. Therapy should be continued for 10 days.

Alpha-hemolytic streptococci (viridans group)—Short-term prophylaxis of bacterial endocarditis prior to dental or other operative procedures in patients with a history of rheumatic fever or congenital heart disease who are hypersensitive to penicillin.

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Treponema pallidum—As an alternate treatment in patients allergic to penicillin.

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Establish susceptibility of pathogens to erythromycin, particularly when *S. aureus* is isolated.

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Known hypersensitivity to erythromycin.

Warnings:

Safety for use in pregnancy has not been established.

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Exercise caution in administering to patients with impaired hepatic function. During prolonged or repeated therapy, there is a possibility of overgrowth of nonsusceptible bacteria or fungi. Surgical procedures should be performed when indicated.

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Please see opposite page for Brief summary

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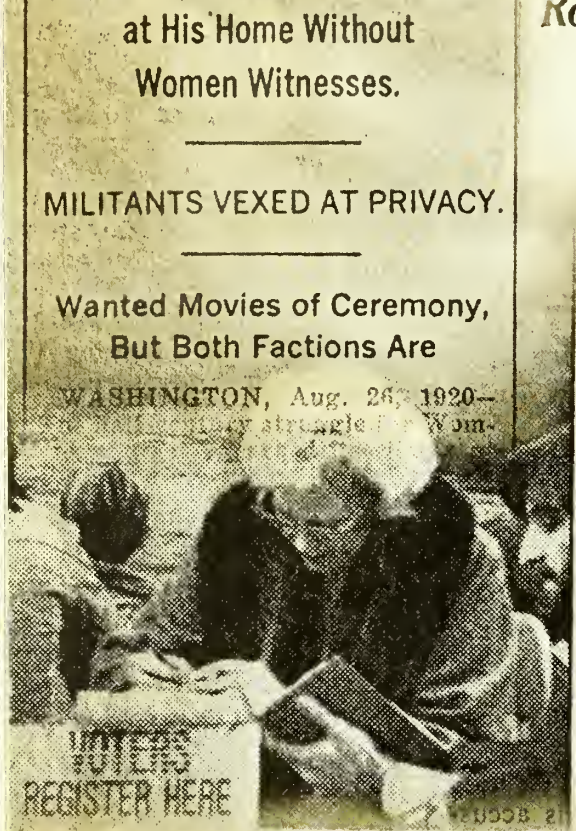
MILITANTS VEXED AT PRIVACY.

Wanted Movies of Ceremony, But Both Factions Are

WASHINGTON, Aug. 26, 1920—



Social Security Bill Is Signed; Gives Pensions to Aged, Job

Roosevelt Approves Message Intended to Benefit 30,0 Persons When States Adopt Cooperating Laws–He the Measure 'Cornerstone' of His Economic Progra

WASHINGTON, Aug. 1 The Social Security Bill, p a broad program of unemp insurance and old age and counted upon to bene 20,000,000 persons, became day when it was signed b dent Roosevelt in the pre those chiefly responsible ting it through Congress.

Mr. Roosevelt call the "the cornerstone in a s which is being b me s comple ri to

SENATE APPROVES 18-YEAR OLD VOTE IN ALL ELECTIONS

Amendment to Constitution is Sent to House, Where Passage is Expected

WASHINGTON, March 10, 1971—The Senate approved today, 94 to 0, and sent to

TRUMAN CLOSES ITED NATIONS CONFEREN WITH PLEA TO TRANSLATE CHARTER INTO DEEDS

NEW WORLD HOPE

President Hails 'Great Instrument of Peace,' Insists It Be Used

HISTORIC LANDMARK

Meeting Gives Standing Ovation as Executive Pictures Peace Gain

"If we fail to use it," he declared to the solemn final meeting of the delegates, 'we shall betray all of those who have died in order that we might meet here in freedom and safety to create it.'

"If we seek to use it selfishly—for the advantage of any one nation or any small group of nations—we shall be equally guilty of that betrayal."

Fervent Interpolation

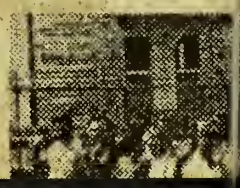
The President, speaking in the auditorium of the War Memorial Opera House, built in memory of sons of the Golden Gate city who gave their lives in the first World War, in which he himself served, seemed to give unconscious expression to the solemn feeling of the occasion when, at the outset of his speech, he interpolated the words, half a hope, half a prayer:

"Oh, what a great day this can be in history!"

Just before the plenary session

SIGN the Dra Ends No

WASHINGTON, Jan. 27, 1973—"With the signing of the peace agreement in Paris today, and after receiving a report from the Secretary of the Army that



PATIENT PACKAGE INSERTS: A CONCEPT WHOSE TIME HAS COME?

The consumer's right to know is an irreversible and desirable trend of the Seventies. It extends, and properly, to a patient's right to know more about his or her prescription medications. One way, gaining favor, is through patient package inserts. Wisely-prepared and properly distributed when medically indicated, they could markedly improve patient knowledge and drug therapy—laudable goals by anyone's standards.

The PMA endorses these goals and will work with government, the health professions and consumers to achieve them.

The Advantages

The concept holds promise of benefits: better patient understanding of the product prescribed, better adherence to the treatment plan, and more awareness of possible side reactions.

Every doctor has had patients who fail to finish antibiotic regimens because they feel better. Some patients assume that if one tranquilizer or analgesic is good, two may be twice as good. Still others fail to report dizziness while on antihypertensive therapy —and so on.

Problems like these might arise less often if the patient received written information in addition to verbal instructions. Some studies suggest that patients are more receptive to such materials, and they more often understand the verbal instructions and follow them, when inserts are used.

The Disadvantages

There are also some potential problems. Obviously, the inserts must be clearly phrased, without extraneous or complex detail. How much information is enough? How can it be kept current? Should all patients receive the same information? Should inserts be included with all drugs? Should only potential problems be listed or are patients better off with a "fair balance" presentation that describes usefulness as well as drawbacks?

These and similar questions require answers, since model inserts have yet to be properly developed and tested. Despite the need for these studies, the FDA is proceeding prematurely with inserts on selected products. We think the Congress is the only place where the matter can be given the proper legal status and direction, particularly since it represents a conceptual change in the legal, medical and social framework of the nation's prescription drug information system.

The Solution

The PMA believes that carefully-devised pilot studies of various kinds of inserts are needed. They should be developed and implemented with full participation by doctors, pharmacists, consumers, communications experts and the drug industry. Such studies will provide reliable pathways to follow, so that inserts will be useful aids to medical practice.

And particularly we think that you should be closely involved in this debate and in these studies and decisions. Otherwise, people with less experience and qualifications may control the purposes, content and use of a tool with considerable promise for improved patient care. It could make a difference in your practice tomorrow, and more importantly, in the health of your patients.

PMA
THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION
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Books Received

(Continued From Page 10)

HUMAN HISTOLOGY—An Introduction to the Study of Histopathology—Third Edition—Dugald L. Gardner, MA(Cantab), MD, PhD, FRCP, FRCP-(Ed), FRCPath, Musgrave Professor and Director of the Institute of Pathology, The Queen's University, Belfast; Consultant Pathologist, The Royal Victoria Hospital, Belfast; and the late T.C. Dodds, FIMLT, FIIP, FRPS, Formerly Director of the Medical Photography Unit, University of Edinburgh. Churchill Livingstone - Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 432 pages, $29.50.

INTERPRETATION OF BIOCHEMICAL MULTITEST PROFILES—An Analysis of 100 Important Conditions—Paul L. Wolf, MD, Professor of Pathology, Division of Clinical Pathology, University of California, San Diego, School of Medicine, La Jolla. Masson Publishing USA, Inc., 14 East 60th St., New York City (10022), 1977. 296 pages, price not listed.

THE JOINTS OF THE ANKLE—Verne T. Inman, MD, PhD, Professor Emeritus of Orthopaedic Surgery, University of California, San Francisco. The Williams & Wilkins Co., 428 E. Preston St., Baltimore (21202), 1976. 117 pages, $12.95.

LABOR AND DELIVERY: AN OBSERVER'S DIARY—What You Should Know About Today's Childbirth—Constance A. Bean. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1977. 202 pages, $7.95.

A LABORATORY MANUAL FOR RURAL TROPICAL HOSPITALS—Monica Cheesbrough, FIMLT, Previously of Nangina Hospital, Kenya; and John McArthur, MRCS, LRCP, Dip RMS, FSIA, The McArthur Microscope, Landbeach, Cambridge; Previously: Director of Malaria Research for North Borneo, Sarawak and Brunei, and Member of W.H.O. Expert Advisory Panel on Malaria. Churchill Livingstone - Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 209 pages, $7.50.

MANAGEMENT OF THE UROLOGICAL PATIENT—Robert Morpeth Jameson, MB, BS(Hons) Durham, FRCS(Eng), Consultant Urologist, Regional Urological Centre, Regional Paraplegic Centre and Liverpool Area Health Authority(Teaching), Sefton General Hospital, Liverpool; K. Burrows, SRN, Renal Transplantation Unit, Liverpool Royal Infirmary; and Beryl Large, SRN, Kidney and Home Dialysis Units, Sefton General Hospital. Churchhill Livingstone - Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 249 pages, $13.50.

METHODOLOGY IN MEDICAL GENETICS—An Introduction to Statistical Methods—Alan E.H. Emery, MD, PhD, DSc, FRCP(E), MFCM, FRS(E), Professor of Human Genetics, University of Edinburgh. Churchill Livingstone - Medical Division, Longman, Inc , 19 West 44th St., New York Cty (10036), 1976. 157 pages, $14.95.

MOTOR DISORDERS OF THE ESOPHAGUS—Robert D. Henderson, MB, FRCS(C), Associate Professor of Surgery, University of Toronto; Chief of Surgery, Women's College Hospital; Consultant Surgeon, Toronto General Hospital and Princess Margaret Hospital, Toronto. The Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202), 1976. 231 pages, $22.50.

OFFICE GYNECOLOGY—Robert H. Glass, MD, Associate Professor in Residence, Department of Obstetrics and Gynecology, University of California, San Francisco. The Williams & Wilkins Company, 428 E. Preston St., Baltimore, MD (21202), 1976. 280 pages, $24.95.

OPHTHALMIC PLASTIC SURGERY—Fifth Edition—Sidney A. Fox, MS-(Ophth), MD, MED SCI D (Hon), Quondam Clinical Professor of Ophthalmology, New York University School of Medicine; Visiting Ophthalmologist, Bellevue Hospital; Consultant Ophthalmologist, Bronx VA Hospital, Goldwater Memorial Hospital, Hospital for Joint Diseases and Medical Center, St. Vincent's Hospital, and Cabrini Medical Center. Grune & Stratton, Inc., Medical and Scientific Publishers, 111 Fifth Avenue, New York City (10003), 1976. 666 pages, $39.50.

PAIN: A PERSONAL EXPERIENCE—J. Blair Pace, MD, Co-chairman, Chronic Pain and Problem Back Service, Rancho Los Amigos Hospital, Downey, California. Nelson-Hall Inc., Publishers, 325 W. Jackson Blvd., Chicago (60606), 1976. 163 pages, $7 95.

THE PATHOLOGY AND SURGERY OF THE VEINS OF THE LOWER LIMB—Second Edition—Harold Dodd, ChM(L'pool), FRCS(Eng), Emeritus Surgeon to St. Mary's Hospital(London) Group, Royal London Homeopathic Hospital, King George Hospital, Ilford and Royal Hospital, Richmond; and Frank B. Cockett, MS(Lond), FRCS(Eng), Surgeon to St. Thomas's Hospital, London. Churchill Livingstone - Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 323 pages, $39.50.

PLASMA HORMONE ASSAYS IN EVALUATION OF FETAL WELLBEING—Edited by Arnold Klopper, PhD, MD, FRCOG, Professor of Reproductive Endocrinology and Honorary Consultant Obstetrician and Gynaecologist, Department of Obstetrics and Gynaecology, University of Aberdeen. Churchill Livingstone - Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 177 pages, $16.00.

RECENT ADVANCES IN GASTROENTEROLOGY—Number Three—Ian A.D. Bouchier, MD, FRCP(Lond), FRCP(Edin), Professor of Medicine, University of Dundee; Department of Medicine, Ninewells Hospital and Medical School, Dundee. Churchill Livingstone - Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 338 pages, $32.50.

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Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude development of ataxia, oversedation or confusion (not more than two capsules per day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacologic effects of agents, particularly potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g , excitement, stimulation and acute rage) have been reported in psychiatric patients. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.
Adverse Reactions: No side effects or manifestations not seen with either compound alone have been reported with Librax. When chlordiazepoxide hydrochloride is used alone, drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are avoidable in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally with chlordiazepoxide hydrochloride, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax are typical of anticholinergic agents, *i.e.*, dryness of the mouth, blurring of vision, urinary hesitancy and constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

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OB-GYN—We are seeking a Board Certified or eligible physician to replace an OB partner lost because of health reasons. We are a 20 physician, multi-specialty group located 55 miles northwest of Chicago in the Chain-O-Lakes resort area with easy access to the city. Our candidate will step into an active three man OB-GYN practice with incentive pay from day one (with a guaranteed minimum draw), malpractice paid, excellent fringe benefits. Our group is physically adjacent to a 144 bed general community hospital and State Trauma Center. Call or write Jim Dickson, McHenry Medical Group, 1110 North Green Street, McHenry, Illinois 60050 - 815/385-1050.

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(Continued on Page 19)

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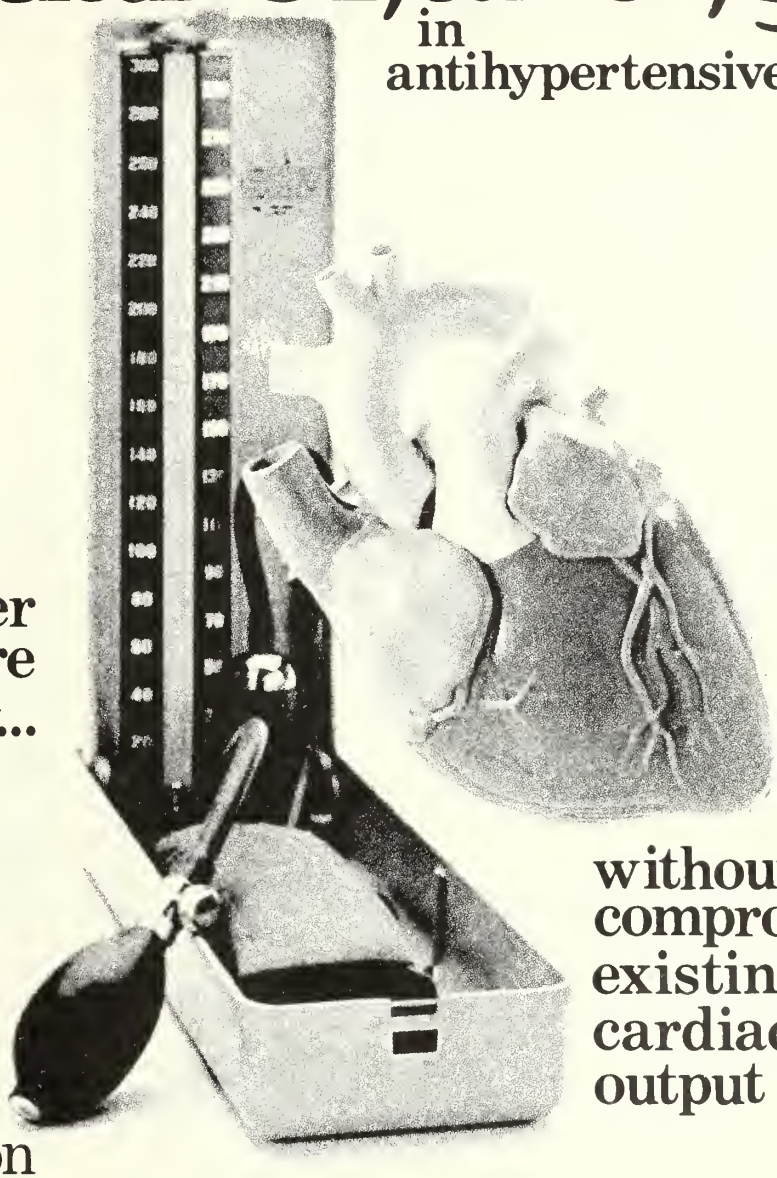

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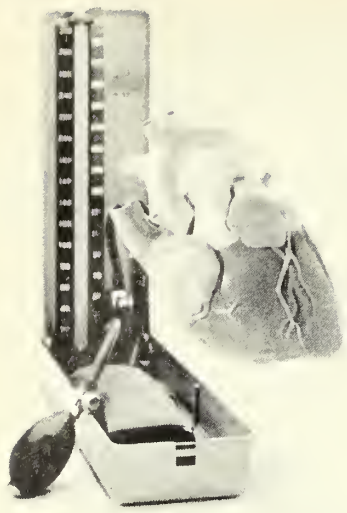

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Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Use in Pregnancy: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks; possibility of fetal injury can not be excluded.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: uric acid by the phosphotungstate method, creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia.

Allergic: Drug-related fever, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third month of therapy; increased dosage or adding a thiazide frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease, this may be avoided by lower doses.

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(Continued from Page 16)

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Refer to: Jergens ME, Morgan MT, McElroy CE: Selective use of radiography of the skull and cervical spine. West J Med 127:1-4, Jul 1977

Selective Use of Radiography of the Skull and Cervical Spine

MARK E. JERGENS, MD; MARSHALL T. MORGAN, MD, *and* CHARLES E. McELROY, MD
Los Angeles

Based on the findings of a five-month study, the authors suggest that physicians should be more discriminating in using radiography of the skull, especially when dealing with patients who are minimally injured. The low incidence of fractures disclosed by radiography in patients with insignificant head injuries is a primary factor in arriving at this recommendation. A lack of correlation between skull fractures, and cerebral injury, and subsequent therapy is another factor. Finally, the prohibitive cost of medical care generally (and radiographs in particular) makes greater selectiveness imperative.

Although the number of cervical spine fractures in this study was small, the findings indicate that based on history and physical examination there can and should be increasing selectivity in ordering routine cervical spine series, without increasing the risk of missed fractures.

THE RELATIVELY LOW YIELD of clinically relevant data derived from skull radiographs in emergency situations was reported by Bell and Loop[1] in 1971 and later corroborated by other authors.[2] Despite this, the skull and cervical spine series continue to be integral to an evaluation of traumatized patients with suspected head or neck injuries regardless of physical findings. In view of the implied inefficiency of this and other radiographic examinations,[3] we undertook a prospective study spanning five months of experience at the University of California at Los Angeles (UCLA) Emergency Medicine Center. From October through December 1975 and from March through April 1976, an investigative effort was made to determine the resident house staff's capability to predict fractures based on physical findings and to evaluate the effects of clinically unsuspected but radiographically shown fractures on patients' clinical course, as well as to establish the clinical indication for ordering skull or cervical spine radiographic series, or both. Criteria for selective ordering of radiographs would obviously reduce the cost of health care yet avoid the risk of litigation resulting from insufficient data having been acquired.

From the Departments of Surgery and Medicine, Emergency Medicine Center, UCLA Hospital, Los Angeles.

Submitted October 20, 1976.

Reprint requests to: Mrs. Seba Kolb, Editor, Department of Surgery, UCLA Center for the Health Sciences, Los Angeles, CA 90024.

Material and Methods

The UCLA Emergency Medicine Center serves a population of about 500,000 people, and is located in a relatively high socioeconomic residential, business and light industrial area. Although flanked by two major freeway systems and serving as a base station for eight paramedic units, there is a preponderance of patients having nontraumatic and minor injuries.

The monthly census seen by the surgical house staff averages 2,500 patients. Residents on duty in the Emergency Medicine Center were asked to complete a questionnaire whenever radiographs of the skull or spine were ordered. This required designating the type of examination, the primary indication for the procedure, the character of any physical findings and the physician's estimate of the probability of fracture being present. Moreover, the radiology resident completed a similar questionnaire dealing with his findings. An attempt was made to exclude data derived from patients with fractures resulting from previous injury. Although some questionnaires were completed retrospectively, missing or incomplete forms were rectified within 24 hours of the event, at the time of daily staff radiographic review. Most such evaluations concerned severely traumatized patients whose clinical condition precluded prospective clerical completeness.

TABLE 1.—*Distribution of Radiographs and Fractures in Each Clinical Category*

Clinical Category	*Total*	*Number Without Fracture*	*Number of Fractures*	*Percent of Fractures*
Skull				
<10%	761	755	6	0.8
50/50%	71	65	6	8.5
>90%	15	6	9	60
	847	826	21	2.4
Cervical Spine				
<10%	510	508	2	0.4
50/50%	55	52	3	5.5
>90%	8	6	2	25.
	573	566	7	1.2

All of the patients with fractures were followed up after a three-month interval by telephone contact either with the patient or his physician, and information about the long-term effects of the fracture on the patient's health was requested.

Results

During the five-month investigation, there were 21 skull fractures in 847 skull examinations (2.4 percent), and seven cervical spine fractures in 573 examinations (1.2 percent). Table 1 compares the clinical prediction of the likelihood of fracture with the percentage of actual fractures in each group. In cases where the clinician believed the probability of fracture to be low, 0.8

TABLE 2.—*Disposition of Patients with Fractures*

Category	*Number of Fractures*	*Follow-up*
Skull		
<10%	6	All placed under observation and then discharged. All have returned to normal lives.
50/50%	6	Three patients placed under observation and then discharged. All have returned to normal lives.
		Two patients with concomitant cervical spine fractures were admitted for treatment of those fractures. One patient with cerebrospinal fluid otorrhea was treated for that and has suffered no sequelae.
>90%	9	Two patients without neurologic deficits were placed under observation and then discharged. Both have returned to normal lives.
		Four patients with concomitant cerebral contusions were admitted to hospital and treated for those contusions. All have returned to normal lives.
		Two patients died after evacuation of subdural hematomas.
		One patient with cervical spine fractures and massive head, chest and abdominal injuries died secondary to those injuries.
Cervical Spine		
<10%	2	One patient admitted to hospital and did well with cervical traction.
		One patient with stable fracture was treated as an outpatient with a brace.
50/50%	3	Two patients admitted to hospital and did well with cervical traction.
		One patient with stable fracture was treated as outpatient with a cervical brace.
>90%	2	One patient died while evacuation of subdural hematoma was being done.
		One patient with concomitant massive head, chest and abdominal injuries died secondary to those injuries.

TABLE 3.—*Reasons for Ordering Radiographs in Patients with Less Than 10 Percent Likelihood of Fracture*

	Number	*Number of Fractures*
Skull Series		
Strictly medicolegal	146	1
Patient or family request	33	0
Physical findings	582	5
Cervical Spine Series		
Strictly medicolegal	132	0
Patient or family request	26	0
Physical findings	352	2

percent of the skull examinations taken actually showed a fracture, and 0.4 percent of all cervical spine examinations in the same category showed a fracture.

Table 2 shows that all patients with less likelihood of fracture (less than 10 percent) were observed for potential neurologic sequelae. In six of the eight patients who had greater likelihood (greater than 90 percent) of skull fracture, significant concomitant cerebral injury was shown. (These percentages are approximations.)

As Table 3 shows, 19 percent of all skull examinations and 26 percent of all cervical spine radiographs were ordered primarily for medicolegal considerations even though in most of the patients concerned there were no suspicious findings at the time of examination. A number of examinations were ordered at patients' request or insistence.

In our total of 847 skull radiographic examinations, 761 were not expected clinically to show fracture, and in fact less than 1 percent of this group did. These six fractures were all linear in nature, and no abnormal neurologic findings were noted at examination of the patients. Each case was handled conservatively with overnight observation of neurologic function followed by subsequent release. In two patients with skull fractures among the 71 patients in the "50-50" clinical category, hemotympanum was present and basilar skull fractures were noted. Three patients in whom only soft tissue swelling and significant tenderness were present over the area of fracture were confirmed as being neurologically stable. In two patients significant cerebral injury was present and they were admitted for treatment. These groups comprised 832 patients or 98 percent of our entire study group; the cost of radiography was $44,000. In all patients, including those with subdural hematomas and those with cerebral contusions, treatment was based on results of neurologic examination rather than on radiographically demonstrated fracture. Every case in which obvious hemotympanum, or cerebrospinal fluid rhinorrhea or otorrhea was present (and hence predictable basilar skull fracture) was similarly managed by following the clinical course and not on the basis of skull film results.

Comments

We believe that the findings of this study substantiate the concept that attention should be directed first to a patient's mental status and neurologic examination rather than to the presence or absence of skull fractures when predicting immediate or long-term neurologic outcome. Our study also shows that 20 percent of these skull films, though lacking in clinical indication, were taken for "insurance" against potential litigation problems rather than strictly for clinical reasons. These data also indicate that a clinician in training usually can accurately predict a skull fracture without radiographs. Indeed, our statistics show a less than 1 percent incidence of unsuspected fracture for 761 patients. Whenever a resident physician believed there was a significant likelihood of injury, he was proven correct 50 percent of the time, therefore allowing a safe margin for error.

On the other hand, the study of cervical spine radiographs is somewhat less conclusive. Although the overall incidence of fractures is low at 1.2 percent, definitive inpatient management was required in three of seven patients because of radiographically shown fractures, while neck braces were fitted in two as outpatients. One patient died while evacuation of bilateral subdural hematomas was being done and the seventh patient seen died after a cerebral injury and massive trauma. Moreover, one of the patients, who had a clinically unsuspected cervical spine fracture, had no significant head injury but was found to have a ruptured spleen as a result of involvement in a motor vehicle accident; this points out the need for cervical spine radiographs when there is a history of significant decelerative accident. The fact that there was a significant concomitant occurrence of cervical spine and head injuries explains why many cervical spine examinations are done in conjunction with radiographs of the skull to determine if head injuries are present despite the absence of cervical spine pathology on physical examination.

The study by Bell and Loop[1] reported findings similar to ours in that the relatively low yield of skull fractures in all patients in whom radiographs of the skull were done was less than 6 percent. They further established that showing the presence of fracture radiographically was not helpful in predicting either short-term or long-term sequelae when compared with physical examinations. Similarly, Piazza and Christi[2] concluded that plain skull radiography itself was insufficient to predict the need for angiography or craniotomy in closed-head injuries. In their review of 100 such cases, the only consistent reliable radiographic sign (significant pineal shift) appeared 20 times; however, in 18 of these patients there also were findings on physical examination that pointed to the side of injury.

Nevertheless, the specter of litigation under which emergency physicians labor is immense, as recent reports[4] show. The standard of practice seems to be to carry out x-ray studies in any and every case of head injury in order to denote fractures, regardless of a patient's neurologic status and whether or not it will alter the patient's therapy.

Although it is beyond the scope of this paper to list all of the indications for skull and cervical spine radiography in emergency situations, we believe that substantial percentages of skull and cervical spine radiographs in this study could have been safely eliminated when there was neither a history of decelerative force, loss of consciousness or other neurologic deficit, nor a finding of notable palpable tenderness on examination of the skull. In patients with serious neurologic trauma, full radiographic workup can be done after stabilization, with neurologic status serving as the barometer of injury.

The question must certainly be raised as to whether the $44,000 allocated in an urban Los Angeles emergency room during the brief time of this study represented a prudent health care expenditure. Would this money be better spent for observation in a greater number of patients for a period of 12 to 24 hours? Should radiographs continue to be taken to show fractures over the course of the middle meningeal artery, so that a patient can be placed under observation to rule out an acute epidural hematoma? Our data showing 556 radiographic examinations without a fracture across the course of the middle meningeal artery and the proven predictability of fracture in this area by physical examination make us think not.

In view of the increasing demands for cost-effective medicine and peer review, we believe that our data raise important health care questions and suggest that improved screening of patients would reduce the number of radiographs required to provide good patient care while at the same time keeping fear of litigation to a minimum.

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4. Professional Liability Newsletter 7, No. 9, Jan 1976

Refer to: Lowitz BB, Benjamin RS: Nononcologic disease in patients with cancer. West J Med 127:5-14, Jul 1977

Nononcologic Disease in Patients with Cancer

BARRY B. LOWITZ, MD, *Sepulveda, California,* and ROBERT S. BENJAMIN, MD, *Houston*

Nononcologic medical problems are common in patients with cancer. Failure to evaluate and treat these problems leads to considerable morbidity and mortality in people who often have potential for both comfortable and productive lives. While a physician is sometimes powerless to prevent the progression of underlying cancer, he must not allow a diagnostic category to color his approach. By seeing only an end point which is inevitable for all people, one could be inclined not to treat what is treatable. With clinical judgment, information and the eternal question of diagnosticians, "What else could this be?", a physician can focus not on the inevitability of death but on the quality of life.

"The aim of science is to seek the simplest explanation of complex facts . . . Seek simplicity and distrust it."

ALFRED NORTH WHITEHEAD

". . . the fallacy of attributing to one cause what is due to many causes."

H. S. JENNINGS

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LIKE SYPHILIS AND SYSTEMIC VASCULITIS, cancer is a great masquerader, often appearing in a cloak of symptoms and signs suggestive of other diseases. Once the presence of malignancy is established, it therefore becomes tempting to attribute all further developments to the cancer. As a consequence, what is thought of on superficial clinical grounds to represent a fatal or untreatable issue of malignancy, may prove at autopsy to be a highly treatable, nononcologic illness. In such a case, timely treatment of the intercurrent problem might have allowed the patient with cancer to return to a functional life for an indefinite period. Conversely, because of many new and effective techniques, cancer may be the only treatable possibility, and its differentiation from untreatable nononcologic disease may be lifesaving. It is the purpose of this article to emphasize the many instances in cases of cancer in which careful evaluation of a patient's problems will significantly improve therapy and prognosis. Particularly in patients in whom malignancy appears to be in control, physicians should always consider other causes for the patients' problems in order to prevent unnecessary morbidity or even mortality which would not be allowed in patients without cancer.

From the Investigative Therapeutics Branch, Hematology-Oncology Division, Department of Medicine, Veterans Administration Hospital, Sepulveda, California, and Developmental Therapeutics, M. D. Anderson Hospital and Tumor Institute, University of Texas System Cancer Center, Texas Medical Center, Houston.

Submitted October 4, 1976.

Reprint requests to: Barry B. Lowitz, MD, Hematology-Oncology Division, Dept. of Medicine, VA Hospital, 16111 Plummer St., Sepulveda, CA 91343.

ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
ADH = antidiuretic hormone
CSF = cerebrospinal fluid
HCG = human chorionic gonadotrophin
PTH = parathormone
TRH = thyrotrophin releasing hormone
TSH = thyroid stimulating hormone
T_4 = thyroxine

Nononcologic Diseases Mimicking Paraneoplastic Syndromes and Malignant Metabolic Disorders[1,2]

Hypercalcemia

Hypercalcemia is produced by a large variety of benign and malignant processes (Table 1). A history of neoplasm is suggestive. However, even when tissue studies show the presence of cancer, this is not adequate proof that the malignancy is responsible. Biopsy proven cancer may coexist with a benign cause of hypercalcemia; differential points to consider are as follows:

- The ingestion of thiazide diuretics may lead to hypercalcemia and provide a readily correctable cause, although hypercalcemia in this setting may be related to an underlying parathyroid excess.[17]
- The development of hypercalcemia in a patient with hilar adenopathy and erythema nodosum should suggest sarcoidosis.[18] Lymph node biopsy studies may help to clarify the diagnosis; however, nonspecific granulomatous change in lymph nodes may coexist with carcinoma,[19-21] and in dubious cases, mediastinoscopy and biopsy may be necessary.[22]
- Hyperthyroidism can cause hypercalcemia and should be considered in patients with sweating, hyperkinetic states and unexplained tachycardias. Thyroid function studies will lead to the correct diagnosis.[5,6]
- Hypercalcemia may develop in a patient with acute adrenal insufficiency. Such a patient may also have orthostatic hypotension, hypoglycemia and hyponatremia; each of which could represent a cancer-related diagnosis.[23] Despite the frequency of adrenal metastasis in several types of tumor, adrenal insufficiency rarely complicates them.
- Primary hyperparathyroidism may appear in patients with cancer. Farr and co-workers have reviewed the cases of 100 patients with hyperparathyroidism; 34 patients had cancer before, coincident with or after the discovery of a benign parathyroid adenoma.[24] The malignant lesions included those of the breast, stomach, lung, pharynx, kidney and thyroid; each of these tumors is known to cause hypercalcemia independently of primary parathyroid disease. Distinction between neoplasm-induced hypercalcemia and that due to primary hyperparathyroidism can be difficult. A history of renal stones, pruritus, peptic ulcer disease or pancreatitis suggests the long-standing parathyroid adenoma; these findings are generally absent in hypercalcemia resulting from malignancy. Parathormone excess can be determined by radioimmunoassay, and newer immunospecific assays may show ectopic parathormone.[25] Farr's group evaluated hypercalcemia with serial alkaline phosphatase, serum calcium and phosphorus, calcium infusion, tubular phosphate reabsorption and prednisone suppression tests. They considered elevated parathormone (PTH) and elevated calcium to be prima facie evidence of primary hyperparathyroidism. In patients with tumors such as breast cancer, small cell lung cancer[26] and carcinoid[27] which do not produce ectopic PTH, the presence of elevated levels of serum chloride and calcium and a decreased tubular phosphate reab-

TABLE 1.—*Causes of Hypercalcemia*

Benign Causes[3]
Thiazide diuretics
Hyperparathyroidism
Sarcoidosis
Hyperthyroidism[5,6]
Acute adrenal insufficiency
Benign monoclonal gammopathy[7]
Milk alkali syndrome[4]
Acromegaly
Hypothyroidism
Renal insufficiency and transplantation
Diuretic phase of acute renal insufficiency
Hypervitaminosis A[8]
Paget's disease

Malignant Causes[9]

Causes	*Responsible Tumors*
Bone metastasis	Many neoplasms
Ectopic parathormone[10]	Epidermoid carcinoma of the lung
	Renal adenocarcinoma[11]
	Oral cavity cancers
	Bladder carcinoma
	Carcinoma of the penis[12]
	Carcinoma of the breast
	Carcinoma of the parotid[10]
	Reticulum cell sarcoma[10]
Abnormal sterol metabolism	Carcinoma of the breast[13,14]
Prostaglandins[15]	Lung cancer
Unknown	Acute leukemia
	Chronic myelogenous leukemia[16]
Estrogen therapy	Carcinoma of the breast

sorption is strong indication to pursue primary hyperparathyroidism. The serum chloride to phosphate ratio has recently been correlated with hypercalcemia due to excessive PTH production either in patients with primary hyperparathyroidism or those with ectopic hormone production. A ratio greater than 32 strongly suggests a parathormone-related cause and makes consideration of parathyroid adenoma a major one in differential diagnosis.[28] It may be possible to show the location of hyperfunctioning parathyroid tissues by venography and venous sampling preoperatively.[29] However, neck exploration may be an essential part of the diagnostic workup when the primary hyperparathyroidism cannot otherwise be excluded. In more obscure cases in which neck exploration is not revealing, selective venous catheterization for PTH radioimmunoassay or showing the presence of PTH in the tumor may clarify the diagnosis.

Tumors produce hypercalcemia both by distant effects (ectopic hormones, prostaglandin E_2, and abnormal sterols) and by direct bone invasion. At present, only ectopic parathormone is amenable to measurement. It may be assayed in blood and tumor.[25] Serum and urine levels of calcium and phosphate, tubular phosphate reabsorption, and urine cyclic adenosine monophosphate (AMP) and creatinine ratios may give indirect evidence of parathormone effect.

Direct tumor invasion of bone may be assessed by serum alkaline phosphatase, bone scan and bone biopsy; these studies should be obtained in the evaluation of hypercalcemia in patients with cancer. When malignancy is established as the cause, hypercalcemia may be controlled by appropriate antitumor therapy. Hypercalcemia may occur during estrogen therapy of breast cancer with bone metastases. This may be a short-lived side effect in an otherwise good tumor response. The addition of cytotoxic chemotherapy or mithramycin may see the patient through this critical metabolic period to a long remission.[30] Alternatively, estrogen withdrawal and adrenalectomy may be of benefit in such tumors with obvious estrogen responsiveness.

Hypocalcemia

Hypocalcemia is uncommon in patients with cancer, but has been reported in patients with osteoblastic metastases from breast cancer and in one patient with chondrosarcoma.[31-33] In patients who have malabsorption syndromes, short bowel syndrome, severe malnutrition, enteric fistulae, prolonged parenteral alimentation or alcoholism, magnesium deficiency and hypocalcemia may develop.[34-37] Replacement of the magnesium in patients with hypomagnesemia may allow the correction of otherwise refractory hypocalcemia.[38,39]

One of us (B.L.) has followed a patient with extensive abdominal carcinomatosis from primary ovarian cancer. In this patient, long periods of nasogastric tube decompression with parenteral alimentation for incomplete bowel obstructions were required. Muscular cramps, carpopedal spasms and Chvostek sign developed in association with hypocalcemia. Despite parenteral administration of calcium gluconate, the blood calcium level could not be stabilized. A serum magnesium level was obtained and was notably depressed. With magnesium supplementation, the calcium concentration returned to normal and the symptoms resolved.

Hyponatremia

While ectopic antidiuretic hormone production may be a consideration in a large variety of tumors and has been shown to be present in tumor extracts,[40,41] many nononcologic conditions may produce hyponatremia, with and without inappropriate antidiuretic hormone (ADH) secretion[42] (Tables 2 and 3). Workup includes determination of urinary sodium concentration and simultaneous urine and plasma osmolalities. Urinary sodium

TABLE 2.—*Inappropriate Antidiuretic Hormone Syndrome*[43-45,51]

Malignancies—especially with mediastinal involvement
Chemotherapy—cyclophosphamide, vincristine[47,48]
Other drugs—morphine, anesthetics
Tuberculosis[49,50]
Other pulmonary infections
Acute intermittent porphyria[46]
Central nervous system lesions
Myxedema
Respirators

TABLE 3.—*Other Causes of Hyponatremia*

Elevated body sodium
Liver disease
Congestive heart failure
Nephrotic syndrome
Decreased body sodium
Adrenal insufficiency
Renal salt wasting
Hyperosomatic non-ketotic coma
Drugs—diuretics, chlorpropamide, carbamazapine, clofibrate, acetominophen

concentration is dependent on intake in the inappropriate ADH syndrome; decreased in nephrotic syndrome, heart failure and liver disease, and usually increased in adrenal insufficiency, diuretic excess, nonketotic hyperosmotic coma and renal salt wasting.

Inappropriate ADH syndromes are also distinguished from other causes of hyponatremia by a low plasma osmolality with a urine osmolality that is not maximally dilute in the presence of normal renal function.[43-45,51] Azotemia, orthostatic hypotension, elevated serum potassium levels and impairment of cortisol increase following adrenocorticotropic hormone (ACTH) administration are features of adrenal insufficiency but not of the syndrome of inappropriate ADH secretion.

Hypokalemia

When hypokalemia develops in patients with small cell carcinoma of the lung, thymoma, nonbeta islet cell pancreatic tumors, cancers of neuroectodermal origin and many other tumors, one should consider ectopic ACTH production.[52] At the same time, one must consider diuretics, alkalosis, long-standing acidosis, and diarrhea or vomiting as causes. In a malignant ACTH syndrome, hypokalemia exists with cachexia, but often without striae or a cushingoid appearance. In the presence of an elevated plasma cortisol value, Cushing disease is distinguished by dexamethasone suppressibility of ACTH and Cushing syndrome by a low plasma ACTH value.

Hyperkalemia

Tumors may cause hyperkalemia by obstruction of the urinary tract. Hypercalcemia or hyperuricemia due to tumor products or tumor therapy may also lead to renal failure. Hyperkalemia may also occur as a consequence of cyclophosphamide therapy in Burkitt lymphoma.[53] Obstruction of the ureters by neoplasm may be readily amenable to radiation or chemotherapy. Nonmalignant causes of hyperkalemia such as drug induced renal failure, acute acidosis, primary acute and chronic renal diseases, Addison disease and radiation strictures of the ureters should be ruled out. The workup consists of urinalysis and determinations of creatinine clearance in serum and electrolytes in urine. Intravenous or retrograde pyelography is necessary whenever obstruction is considered. Dialysis may be required if conservative measures fail to correct the electrolyte imbalance.

Hyperthyroidism

Symptoms and signs of thyrotoxicosis may be found in patients with embryonal tumors, choriocarcinoma[54] and hydatid moles. Evidence of the tumor is usually obvious. In one case followed by us, the patient had a gestational choriocarcinoma with widespread metastasis to the liver, lungs and brain. The presenting features were high fever, sinus tachycardia and tremors. These symptoms responded to propranolol and methimazole. A serum thyroxine (T_4) level was elevated. The patient expired from the extensive cancer before other studies could be undertaken. The diagnosis can be confirmed by the finding of thyroid stimulating hormone (TSH) or thyrotrophin releasing hormone (TRH) in the tumor tissue.

Distinguishing a functioning metastatic thyroid malignancy from other forms of hyperthyroidism is accomplished by the findings of low plasma TSH and total body I^{131} scan[55] and other evidence of organ metastasis such as on x-ray studies of the chest and bone scans.[56]

Hyperlipidemia

Hyperlipoproteinemias of types I and IV have been found in association with some leukemias and lymphomas; types I, III, and V with dysglobulinemias such as macroglobulinemia, myeloma and lymphoma, and type II with nephrotic syndrome complicating certain neoplasms such as Hodgkin disease. These syndromes are not difficult to distinguish and when tumor-related, respond to successful tumor therapy.

Hypoglycemia

The problem of hypoglycemia may complicate insulinoma, retroperitoneal tumors, and primary or metastatic cancer of the liver.[57] In patients with known cancer, possible benign causes include overdose of insulin or oral hypoglycemic agents; hepatic, pituitary or adrenal insufficiency.

Retroperitoneal tumors are usually obvious causes of hypoglycemia because of their characteristically large mass. We have seen one such patient with extensive retroperitoneal hypernephroma who died as a result of hypoglycemia, refractory to glucagon and even continuous infusion of dextrose. However, the more common retroperitoneal malignancies which cause hypoglycemia are sarcomas (for example, hemangiopericytoma, fibrosarcomas). Surgical procedures that reduce the bulk of these tumors alleviate the hypoglycemia. Finding such tumors at operation is usually

TABLE 4.—*Potential Causes of Gastrointestinal Bleeding in Patients with Cancer*

Malignant erosion into the gastrointestinal tract
Peptic ulcer disease
Gastritis—corticosteroids, aspirin, ethanol, phenylbutazone, reserpine, indomethacin, stress
Esophagitis—reflux, chemical corrosive ingestions (suicide attempt), lower esophageal tears following prolonged emesis
Esophageal varices
Bleeding from colonic diverticulum (may be associated with stricture which resembles carcinoma radiographically)
Colitis—ulcerative, shigella, amoeba
Ischemic bowel disease with infarction
Intussusception and volvulus
Thrombocytopenia or coagulopathy

sufficient proof of the cause of this type of hypoglycemia. Similar considerations apply to primary or metastatic hepatic cancer where nodular hepatomegaly, abnormal results on liver function studies and positive findings on biopsy make the cause of hypoglycemia obvious. Appropriate therapy of the tumor per se is the optimal approach to management of this form of hypoglycemia.

Gynecomastia[58]

Ectopic luteinizing hormone may be produced by a variety of types of cancer of the lung[59] and human chorionic gonadotrophin (HCG) from trophoblastic and nontrophoblastic cancer.[60-62] Of this last group, liver, stomach, pancreas, breast, adrenal and renal malignant lesions, myeloma and melanoma are interesting examples. The benign entities to consider, especially in older men with gynecomastia, include the use of certain drugs (digitalis, reserpine, chlorpromazine, spironolactone, dilantin),[63,64] cirrhosis and hemodialysis.[58,65] In the absence of a suggestive drug history, urine or serum determinations of HCG and other mammatropins can be most revealing.

Medical Diseases Mimicking Organ Involvement by Tumors

Gastrointestinal Tract

Upper Gastrointestinal Bleeding. In advanced carcinoma, including that involving the stomach, bleeding is often not related to the tumor. In 81 patients in whom endoscopy was done for upper gastrointestinal bleeding, Lightdale and coworkers[66] found tumors in 72 percent. Of the patients with tumors, 43 percent had hemorrhagic gastrititis, 22 percent had chronic peptic ulcer and 17 percent had direct tumor bleeding. Of 18 patients with stomach tumors, only in ten was the direct source of the bleeding due to the cancer (Table 4).

The thorough evaluation of patients is mandatory, especially in a patient with cancer whose only life-threatening complication is bleeding. Early endoscopy should be considered strongly, and coeliac angiograms may also be indicated. Management should then bear the same indications as for any other patient. Death by exsanguination is an unacceptable alternative to potential months or years of productive life in a patient with limited, though unresectable cancer.

Intestinal Obstruction. In a review of 117 cases in which intestinal obstruction later developed in patients previously treated for cancer, Ketchum and associates found that in 27 percent it was not related to recurrence of or metastasis from the original tumor.[67] In 9 percent there was a new, and often resectable, primary tumor, and in 18 percent there was no evidence of abdominal carcinoma. In three fourths of the remainder, significant palliation was achieved by operative intervention.

Nonmalignant ileus might result from vascular disorders, electrolyte disturbances, adhesive bands, perforated viscus and pancreatitis. Patients with ileostomies, ileal loops and various conditions associated with prolonged diarrhea or vomiting may become sufficiently hypokalemic for ileus to develop. Appropriate management of nonobstructive ileus can usually be accomplished medically. Obstruction should be managed as for any other patients, with tube decompression for low-grade obstruction and surgical operation for high-grade obstruction. Obstruction due to tumor, such as ovarian carcinoma, may respond to chemotherapy.

Liver Disease. In patients with cancer in whom jaundice or hepatomegaly is present and findings on scan or liver function tests are abnormal, hepatic metastasis is not necessarily present. Various infectious diseases and benign infiltrative conditions may revert either spontaneously or with specific therapy. Hepatic uptake of isotope in the left lobe may be decreased following abdominal radiation therapy for Hodgkin disease. Liver biopsy will often settle the issue. The finding of cancer may offer a better chance of response to therapy and, therefore, may offer a better prognosis than the finding of advanced cirrhosis.

Pancreas. Pancreatitis may be associated with malignancy. Other causes such as drugs (glucocorticoids, isoniazid, thiazides, indomethacin, 6-

mercaptopurine, azathioprine, oral contraceptives, L-asparaginase or salicylates),[68-72] should be considered. However, hypercalcemia, ethanol ingestion and a variety of infections are more likely.[73] Hyperamylasemia with circulating macroamylase has been described in bronchogenic carcinoma[74] and can be documented by finding an elevated serum amylase value with a normal urinary amylase level in the presence of normal renal function. Primary or metastatic cancer of the pancreas can lead to pancreatitis.[75,76] The differential diagnosis is aided by a medication history, serum calcium levels, and the serum-to-urine ratio of amylase, which is low in pancreatitis and elevated in macroamylasemia.

Bones

Positive bone scans can be produced by osteomyelitis, Paget disease, hyperostosis frontalis interna, regional osteoporosis, various arthritides, aseptic bone necrosis, postoperative healing and ankylosing spondylitis.[77] In tumors, the scan may be positive in the absence of radiographic findings.[78,79] In their review of 111 cases, Hopkins and Kristensen[77] showed that the scan may be positive in asymptomatic patients with normal values for alkaline phosphatase. A normal alkaline phosphatase value cannot be relied upon to rule out bone metastasis, and occasionally a negative scan is associated with a positive bone biopsy.[80] In a patient with cancer who has bone pain and in whom there are equivocal findings on bone films, scans and serum alkaline phosphatase studies, bone biopsy is essential. The finding of tumor in such a painful site will lead to the institution of important palliative radiation or chemotherapy and a much more comfortable and functional patient.

Lungs

Several nonmalignant diseases may produce radiologic findings compatible with cancer.[81] These include various infections and pneumoconioses. Interstitial disease may mimic lymphangitic dissemination of tumor. In the face of possible interstitial fibrosis due, for example, to bleomycin, busulfan or nitrofurantoin, or having an unknown cause, a biopsy showing lymphangitic cancer will provide evidence for a potentially treatable cause.

Sarcoidosis,[22] mycobacterial, fungal, and protozoal infections[82] may produce pulmonary infiltrates resembling nodular as well as lymphangitic metastasis.[83] Sickles and associates[84] described three cases in which patients with "obvious pulmonary metastases" had benign intrathoracic processes. When the diagnosis is not certain, the same approach should be used as in patients without evidence of cancer and includes skin tests, sputum cytology and culture, mediastinoscopy and, in many cases, open biopsy. Clues to the nonmalignant nature of the infiltrate may be an atypical presentation; for example, pulmonary lesions without hepatic metastasis in a patient with colon carcinoma or "lymphangitic metastases" noted on x-ray studies in an asymptomatic patient.

Heart

In patients with congestive heart failure and arrhythmias unresponsive to the usual management, as well as evidence of carcinoma of the breast, melanoma, oat-cell carcinoma of the lung or histiocytic lymphoma, the only potentially reversible condition may be the tumor. Establishing directly the presence of myocardial metastasis is exceedingly difficult, other than at autopsy. The absence of other causes such as hypertension and atherosclerosis may be clues. The development of unexplained arrythmia or heart block in a patient known to have potentially cardiotropic tumors such as melanoma and small cell lung cancer is strongly suggestive evidence. When all else fails, and if the particulars of the situation require heroic efforts, a trial of chemotherapy or cardiac irradiation might be given with potentially gratifying results.[85]

Malignant pericardial effusions or constrictive pericarditis such as those due to metastatic breast cancer might well respond to low-dose radiation therapy or chemotherapy. On the other hand, pericarditis itself may be due to previous radiation therapy.[86] If tamponade or constriction is the only life-threatening problem, a pericardial window or decortication should be done.[87] Effusions may also be controlled by local instillation of sclerosing agents.

In a patient with heart failure, one must consider the late effects of adriamycin and daunorubicin therapy as possible causes, particularly with cumulative doses exceeding 550 mg per sq meter. With simultaneous cyclophosphamide or with cardiac irradiation, congestive heart failure may occur at even lower doses.[88] In most patients with anthracycline-induced cardiomyopathy there is a decrease in limb-lead QRS voltage of at least 40 percent compared with a pretreatment tracing.[89] Other causes for congestive heart failure should

TABLE 5.—*Azotemia in Patients with Cancer*

Prerenal
Volume depletion
Addison disease
Congestive heart failure
Severe protein loss—gastrointestinal or renal
Renal vascular occlusion
Hepatic failure
Nephrocalcinosis
Uric acid nephropathy
Drug induced—gentamicin, kanamycin, streptozotocin, phenacetin, high dose methotrexate, etc.
Glomerulonephritis—acute and chronic forms
Nephrotic syndrome—Hodgkin disease, colon carcinoma
Postrenal
Stones—calcium, cystine, uric acid, mixed
Stricture—radiation, tumor
Bladder outlet obstruction—prostatic hypertrophy, neurogenic bladder, foreign body

be considered more likely in the absence of this finding.

The following is an example in point. One of us (B.L.) has seen a patient with thymoma in whom pericardial effusion and life-threatening tamponade developed one year after radiation therapy. The pericardial fluid cytology was interpreted as class V. Biopsies of the pericardium and adjacent ribs showed only inflammatory changes consistent with previous radiation therapy. An assumption of uncontrollable malignancy may well have cost the patient's life.

Kidneys

The nephrotic syndrome has been associated with Hodgkin disease, lung cancer, colon cancer, inferior vena cava obstruction and renal vein thrombosis.[90,91] Radiation nephritis, radiation induced constrictive pericarditis, amyloidosis and of course primary renal disease are other causes for the nephrotic syndrome in patients with cancer. Previous chest irradiation may rarely lead to constrictive pericarditis with nephrotic syndrome. A search for clinical and radiologic evidence for constrictive pericarditis and, where indicated, a renal biopsy should be carried out. Collagen vascular disease complicated by cancer may respond to immunosuppressive therapy. In a patient with a history of abdominal irradiation for cancer, hypertension may develop from radiation nephritis, but appropriate workup should be done to rule out other causes for hypertension. The causes of azotemia are legion, and their investigation should include consideration of the prerenal and postrenal types (Table 5).

Nervous System

In a patient with cancer in whom there is clinical evidence of brain metastasis, the brain scan is the most convenient diagnostic method to uncover the lesions. Equivocal cases may be aided by angiography. More recently, the use of computerized axial tomography, especially when combined with intravenous injection of radiopaque contrast medium, has provided more sensitive and selective evidence of brain metastasis.[92]

In high risk groups of patients—such as those with evidence of cerebrovascular disease, those in whom there is evidence of multiple or surgically inaccessible metastatic lesions, or patients in whom there are very strong clinical grounds on which to suspect metastasis, the use of radiation therapy has a much better risk:benefit ratio than the more aggressive surgical approach. Some patients may present with scan and angiographic evidence of a space-occupying lesion in the central nervous system and no other evidence of cancer by history, by laboratory and radiologic evaluation or by analysis of cerebrospinal fluid. In this group, cytocentrifuge study of the spinal fluid should be done. If results are negative, craniotomy must then be considered.

Elevations of intracranial pressure with papilledema secondary to benign conditions may manifest very much like metastatic or primary brain tumors with headaches which are worse in the morning, aggravated by coughing or straining, blurred vision, and sixth nerve palsy. Acute adrenal insufficiency, hypoparathyroidism, hypervitaminosis A, sinus thrombosis, otitic hydrocephalus, and carbon dioxide retention should be considered in the differential diagnosis.

While brain scan and computerized axial tomography are sensitive indicators of the presence of mass lesions, there is a large variety of distant effects on the nervous system by tumors[93,94] (Table 6). As there are no available tests by which these effects can be ruled in, it is the obligation of the physician to rule out the other treatable causes.

Muscles

While muscle weakness and wasting may represent the myasthenic syndrome described by Eaton Lambert, dermatomyositis[97] or the cachexia-anorexia syndrome, one must exclude problems related to electrolyte imbalance. One of our recent patients who had received radiation therapy for thyroid cancer experienced severe weight loss and

weakness which turned out to be due to excess intake of dessicated thyroid. The symptoms subsided when the dosage was reduced. True myasthenia gravis may be present and is distinguished from the Eaton Lambert syndrome by its involvement of the facial musculature, the decrease rather than increase in strength with repeated contractions and its response to edrophonium chloride solution (Tensilon®) rather than guanidine. Muscle weakness may be associated with thymoma or pancreatic carcinoma.

Systemic Problems Mimicking Cancer

Fever

Fever may be found in patients with retroperitoneal tumors, hepatocellular carcinoma, cancer metastatic to the liver, renal carcinoma, Ewing sarcoma and malignant lymphomas.[98] Even in these circumstances, infection remains the most important consideration.[99,100] In patients with solid tumors involving the abdomen, fevers occasionally result from intra-abdominal abcesses. Evaluation with plain abdominal films, B-mode ultrasound scans, liver-lung scans, and gallium scans may show the site of infection for surgical drainage. Patients with extrahepatic obstructive jaundice due to cancer are prone to ascending cholangitis or portal thrombophlebitis. Here, surgical relief of the obstruction can be lifesaving. In the compromised host, one should proceed with empirical antimicrobial therapy immediately after obtaining routine cultures, even in the absence of a demonstrable cause of fever.[100,101] In leukopenic patients, one must pay particular attention to the possibility of perirectal and pelvic abscesses requiring drainage.

In patients with pneumonitis and no clearly demonstrable pathogen after transtracheal aspiration, lung biopsy must be strongly considered. The risk of death from pneumonia caused by Pneumocystis carinii, Candida albicans, aspergillus, Nocardia or Mycobacteria tuberculosis often exceeds that of this surgical procedure, even in patients with compromised pulmonary function.[102] Fever due to the pyrogenic tumors may respond to administration of indomethacin[103] and those due to fungal infections to prednisone.

Central nervous system infection with Toxoplasma gondii[104] and Cryptococcus are important

TABLE 6.—*Effects of Cancer on the Nervous System*

Direct	*Tumors*
Focal neurologic deficits	Most types
Spinal cord Limb weakness, especially hands spacticity, increased reflexes in lower extremities	Lung, breast, stomach "reticulum cell sarcoma"
Compressive neuropathies of peripheral nerves	
Indirect	
Sensory neuropathy[95]	
Encephalomyelitis Loss of recent memory, hallucinations, seizures, confabulation. Spinal fluid may be normal (40 percent) or have increased protein and round cells.	Oat cell carcinoma of the lung involving frontal, temporal lobe or limbic system
Dementia Diffusely slow electroencephalogram Loss of recent memory	Lung, ovary
Subacute cerebellar degeneration Dysarthria, ataxia, hypotonia dementia No nystagmus No focal signs	Lung, ovary, Hodgkin disease and breast
Peripheral neuropathy Distal weakness, decreased depth Tendon reflexes May respond to steroids	Lung, myeloma, Hodgkin disease[95]
Motor system syndrome Focal amyotrophy or upper limb weakness and fasciculation with increased lower limb reflexes and Babinski signs	Lung[96]
Subacute necrotic myelopathy Rapidly destructive hemorrhagic disease, death in weeks	
Cerebrovascular accidents Due to hypercoaguable states, thrombocytopenia Hyperviscosity syndromes	Pancreas, prostate, lung
Infections	
Slow virus syndromes Progressive multi-focal Leukoencephalopathy	Lymphomas, leukemia

treatable causes of fever in immunologically compromised patients. Low cell counts, high protein and negative cultures in the cerebrospinal fluid (CSF) suggest toxoplasmosis. Serologic tests may confirm the diagnosis. Patients with cryptococcosis may not have organisms apparent on India ink preparations of the CSF. In such cases, CSF and urine cultures may show the presence of the organism. Testing CSF for the polysaccharide antigen of Cryptococcus may be of help in establishing the diagnosis.

Blood

Anemia of patients with cancer may be of "chronic disease" type or autoimmune in nature; however, iron deficiency from occult gastrointestinal bleeding or secondary to anticoagulation often complicates the course of these patients. Clearly, the other common causes of anemia must be considered: folate deficiency, pernicious anemia, drug-induced hemolysis including hemolysis due to alkylating agents,[105] hemoglobinopathies and malabsorption syndromes. On the other hand, myelophthisic anemia, drug toxicity and hemolysis due to hypersplenism are problems found in cancer patients. Evaluation should include examination of the peripheral smear, stools for occult blood, serum iron and iron binding capacity, bone marrow aspiration and biopsy, and spleen scan. Similar considerations hold for platelets and granulocytes. The problems of marrow invasion, myelotoxicity, and hypersplenism significantly affect therapy: for the first, increasingly aggressive chemotherapy; for the second, withholding chemotherapy; for the third, consideration of splenectomy.

Lymph Nodes

Lymphadenopathy occurs in a large variety of settings and may be confused with cancer. One must consider a toxic effect of drugs such as the hydantoins,[106] various infectious causes, collagen vascular diseases and even heroin addiction[107] in the differential diagnosis. Although lymphomas may be difficult to distinguish histologically from these benign conditions, biopsy results frequently will settle the issue. In patients with asymptomatic bilateral hilar adenopathy and negative findings on physical examination, biopsy confirmation of sarcoidosis may not be necessary in otherwise asymptomatic persons,[18] but in patients with a history of cancer, biopsy may be essential for the proper diagnosis.

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Moderator
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Discussants
PAUL I. TERASAKI, PhD
EUGENE V. BARNETT, MD
MARY C. TERRITO, MD
JAMES R. KLINENBERG, MD
ROBERT S. PETERS, MD

An edited transcription of an Interdepartmental Clinical Case Conference arranged by the Department of Medicine of the University of California, Los Angeles, School of Medicine.

Familial Mediterranean Fever

Recent Advances in Pathogenesis and Management

The success of colchicine therapy in the management of familial Mediterranean fever has provided new direction to investigations into the pathogenesis of this disease. Examination of HLA antigen frequencies in 53 patients with familial Mediterranean fever and appropriate controls, as well as various immunologic studies have yielded no significant differences. However, B lymphocyte typing and assays for immune complexes, lymphokines and prostaglandins may be of potential interest. Preliminary studies indicate that leukocytes of patients with familial Mediterranean fever release increased amounts of lysozyme ($P<0.01$), when subjected to high temperatures, and of both lysozyme and myeloperoxidase at low osmotic concentrations. The known and potential effects of colchicine on leukocyte and cellular metabolism, and the current status of colchicine prophylaxis are reviewed. In patients receiving an optimum colchicine dose of 1.5 to 1.8 mg per day, side effects have been minimal and the frequency of attacks has been decreased significantly.

ARTHUR D. SCHWABE, MD:* *Familial Mediterranean fever* (FMF) *had long been regarded as a rare and mysterious disorder found primarily in Armenians, Jews and Arabs. Many names,*† *emphasizing one or more of the clinical features, have been applied to this disease. Although a case report of familial Mediterranean fever appeared in 1908,*[1] *Siegal,*[2,3] *Heller, Sohar and Sherf,*[4] *and Sohar and associates*[5] *deserve credit for clearly defining the clinical manifestations of this entity.*

During the past 15 years, more than 1,000 cases of familial Mediterranean fever have been reported from countries of the Mediterranean littoral and beyond. The ethnic origin of 197 patients studied at the University of California, Los Angeles, Hospital is listed in Table 1. A positive

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†Armenian disease, benign paroxysmal peritonitis, periodic disease, perioditic peritonitis, familial recurring polyserositis, familial paroxysmal polyserositis.

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TABLE 1.—*Patients with Familial Mediterranean Fever at the University of California, Los Angeles, Hospital*

Ethnic Origin		*Number*
Armenians		131
Jews		40
Ashkenazic	11	
Non-Ashkenazic	27	
Unknown	2	
Arabs		6
Greeks		3
Italians		4
Turks		3
Miscellaneous		10
Total		197

TABLE 2.—*Diagnostic Criteria of Familial Mediterranean Fever*

Major
Recurrent attacks of
Fever (1-3 days)
Peritonitis (1-3 days)
Pleuritis (1-3 days)
Arthritis (1-30 days)
Erysipeloid-like erythema
Armenian, Jewish or Arab ancestry
Positive family history
Minor
Arthralgias (1-30 days)
Protracted, sero-negative arthritis
Abdominal pain without peritonitis (1-3 days)
Onset before age 20
Remission during pregnancy
Autosomal recessive inheritance
Favorable response to colchicine

family history can be obtained in approximately 50 percent of cases. The irregularly occurring attacks may vary in frequency from one to two per week to one a year. Prolonged attack-free intervals have been recorded in untreated patients.

Clinical manifestations usually begin in childhood, occurring before the age of 20 years in more than 80 percent of the patients.[4,6] *The diagnosis is based on well-defined criteria elicited from the clinical history. The major and minor criteria we use for a positive diagnosis are listed in Table 2. Recurrent, self-limited episodes of fever and inflammation of one or more of the serosal membranes constitute the most significant diagnostic features. The abdominal pain may vary from mild discomfort with localized tenderness to severe, generalized peritonitis with board-like rigidity. The chest pain, which is pleuritic in nature, may be accompanied by pleural effusions. Attacks of fever and peritonitis or pleuritis characteristically last from 12 to 72 hours and are followed by variable periods of complete well-being. Less commonly the fever may be accompanied by arthralgias or frank arthritis, usually limited to one large joint. Symptoms of joint inflammation may persist for longer periods, sometimes for several months, but usually terminate spontaneously and rarely leave any residual joint damage. Complete symptomatic remissions occur in some patients during pregnancy.*

No laboratory abnormalities specific for FMF *have been detected to date. During attacks the leukocyte count, sedimentation rate and values for C-reactive protein, seromucoid, plasma fibrinogen, lipoproteins and haptoglobins are usually elevated.*[3-6] *Complications of* FMF, *which are consequences of difficulty in arriving at the correct diagnosis and the injudicious use of drugs, include multiple laparotomies, narcotic addiction and emotional disturbances. In afflicted Arabs and non-Ashkenazic Jews, but not in Armenians, there is a high incidence of amyloidosis, terminating in renal failure and death.*[4-6] *Early attempts to prevent or abort the febrile paroxysms with a variety of drugs were unsuccessful. Rigid restriction of dietary fat intake reduced the frequency of attacks in some, but not all, patients. The most efficacious drug in preventing attacks has been colchicine.*

The following discussants will review aspects of pathogenesis and management of this disease. Dr. Paul I. Terasaki will examine the incidence of HLA *specificity. Dr. Eugene V. Barnett will summarize the immunological studies done to date. Dr. Mary C. Territo will report on the results of her studies of leukocyte function. Dr. James R. Klinenberg will review the metabolic effects of colchicine. Finally, Dr. Robert S. Peters will bring us up-to-date on the status of colchicine prophylaxis in familial Mediterranean fever.*

Incidence of HLA Specificities

PAUL I. TERASAKI, PhD*

IT IS NOW generally accepted that specific HLA antigens or haplotypes may be associated with certain diseases, the most notable association being the high incidence of HLA-B27 with ankylosing spondylitis.[7] This B27 association is well enough established to be used as an aid to clinical diagnosis of ankylosing spondylitis and related

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diseases. As familial Mediterranean fever is a disease prevalent among Mediterranean populations, and seems to have a high incidence in related family groups, we tried to determine if any HLA association (indicating possible genetic markers for the disease) existed.

Using the microdroplet lymphocytotoxicity test, 53 patients with familial Mediterranean fever and appropriate controls were tissue-typed for HLA antigens. The patients included 40 Armenians and 13 Jews and Arabs from Southern California. The controls, consisting of 82 unrelated Armenians and 94 unrelated Jews, were compared with normal Caucasian controls to determine whether substantial frequency variations existed (Table 3). With some antigens, both Armenian and Jewish populations differed from other Caucasians, that is, lower in B7, B8 and BW40, and higher in BW35. In other antigens, only one population varied. Jewish controls were high in A10; Armenians were higher in A11, AW23, B5 and BW21, and lower in A2 and A29. Because of these variations in frequency, normal Armenian or Jewish controls, or both, were subsequently used in all comparisons in this study.

When Armenian controls were used for comparison, Armenian patients were found to have several antigens that varied considerably in frequency (that is, A3, B13, BW17), but no difference in antigen frequencies was statistically significant (Table 3). The combined group of patients (Armenians, Arabs and Jews) also showed no significant deviation from these controls, either with the total number of patients or with the division by sex. Comparison of each patient group with a normal Jewish control population showed no statistically significant differences in antigen frequencies between patients and controls. The control groups of Jewish and Armenian normals were combined to give a control group approximately equivalent to the combined patient group. When these combined control and patient groups were compared, they showed no statistically significant differences among their antigen frequencies (Table 3). This lack of significant difference was also apparent in comparisons of the combined controls with the combined patients divided by sex and with the Armenian patient group. The analysis does not indicate any trends toward disturbance in antigen frequencies.

TABLE 3.—*HLA Antigen Frequencies in Normal and Familial Mediterranean Fever Populations*

	Frequencies					
	Normal				*FMF*	
HLA Antigen	*Caucasian N=3896*	*Jewish N=94*	*Armenian N=82*	*Combined Jewish and Armenian N=176*	*Armenian N=40*	*Combined Jewish and Armenian N=53*
A1	31%	16%	22%	19%	18%	23%
A2	47	50	29	40	45	47
A3	27	16	28	22	22	19
A10	11	26	7	22	15	15
A11	12	11	21	15	12	9
A28	8	12	11	11	5	8
A29	7	12	1	7	5	4
AW23	3	0	15	7	15	11
AW24	12	7	18	21	22	24
AW30	10	9	7	8	15	17
AW32	7	5	7	6	8	6
AW33	1	0	2	1	2	2
B5	10	10	27	18	25	19
B7	25	11	2	7	8	6
B8	21	9	5	7	10	11
B12	26	20	13	17	22	19
B13	4	7	12	10	2	6
B14	9	17	10	14	5	9
B18	8	10	11	10	22	21
B27	7	5	4	5	0	0
BW15	10	7	5	6	2	4
BW16	9	13	6	14	8	8
BW17	9	10	10	10	0	6
BW21	5	5	20	12	18	17
BW22	4	4	2	3	5	6
BW35	19	27	27	27	38	36
BW37	1	0	2	1	0	0
BW40	12	5	6	6	5	4

We must conclude, therefore, that any genetic marker for familial Mediterranean fever is completely unrelated to HLA antigens. However, B lymphocyte typing is currently being investigated and may shed some light on the susceptibility to this disease.

Immunological Studies

EUGENE V. BARNETT, MD*

FOR SEVERAL YEARS various immunological studies in patients with familial Mediterranean fever have been done at UCLA and other institutions. Repeated searches for LE cells, antinuclear antibodies, or antithyroid antibodies have failed to yield positive results.[2-5,8] Complement and B_1C complement component titres, examined by Ehrenfeld, Eliakim, and Rachmilewitz,[8] and by T. C. Owens, MD in our laboratory (unpublished data, 1970), were found to be within normal limits. Rheumatoid anti-IgG serology tests (such as the F II tanned cell hemagglutination, the sensitized sheep cell and heterophile antibody tests) and latex fixation test for rheumatoid factor have shown no significant elevations.[8,9]

Quantitative changes in serum immunoglobulin levels, particularly significant elevations of IgM, were detected in all of 25 patients studied by Frensdorff and colleagues.[9] In 22 of our patients the mean serum immunoglobulin levels were compared with those of normal controls. Statistically our patients showed significant elevations of IgM ($P<0.001$) and IgG ($P<0.05$).

Although these studies have done little to elucidate the nature of this disease, the application of various newer techniques (such as assays for lymphokines, prostaglandins and immune complexes, and testing for delayed hypersensitivity) may be of potential value.

Leukocyte Function

MARY C. TERRITO, MD†

THE PHAGOCYTIC LEUKOCYTES are important elements of febrile and inflammatory diseases. These leukocytes release proteolytic enzymes, such as collagenase and elastase. They also produce mediators that affect the complement and kinin systems and therefore incite inflammation.[10] The production of a febrile response in man seems to be mediated through the release of endogenous pyrogen, which is also a product of the phagocytic leukocytes.[11]

Although colchicine can affect many cell types, its major clinical activity, at least in acute gout, is thought to be related to its inhibitory effects on granulocyte movement and metabolism, and possibly to lysosomal stabilization.[12] We tend to think of febrile and inflammatory responses as always being secondary to some active inciting agent—be it microbe, immune complexes or chemical compounds. However, there is the theoretical possibility that a leukocyte defect plays a role in the pathogenesis of inflammatory reactions; the cell may be hypersensitive to minor stimuli or it may release its contents at an abnormal or accelerated rate.

No specific etiologic agent has been found in familial Mediterranean fever to date. We have been investigating the status of the neutrophil in familial Mediterranean fever because of (1) the significant neutrophilia of effusions and peripheral blood, (2) the effectiveness of colchicine and (3) the known ability of granulocytes to elicit an inflammatory response.

Investigations pertaining to the functional status of neutrophils from patients with familial Mediterranean fever have shown that these cells react normally in their ability to phagocytize Staphylococcus aureus, to kill Candida albicans, and to migrate randomly or in response to a chemotactic stimulus. The ingestion of colchicine in the doses used in familial Mediterranean fever does not seem to alter the neutrophil function in these standard assays.[13,14] Neutrophils from patients with familial Mediterranean fever have also been found to produce normal amounts of endogenous pyrogen.[14]

In order to investigate the sensitivity of the FMF leukocyte, we have started to study the effects of various stresses on the release of lysosomal enzymes from these cells. We have used lysozyme, and in some cases myeloperoxidase, as marker enzymes, and have subjected the cells to incubation at temperatures from 37°C to 46°C, to osmotic concentrations of 0.3 to 0.9 percent sodium chloride and to pH changes ranging from 6.8 to 8.6. In addition, we have subjected these leukocytes to traumatic stress by incubating them with glass beads on a rocker panel, and to phagocytic stress by allowing the cell suspension to in-

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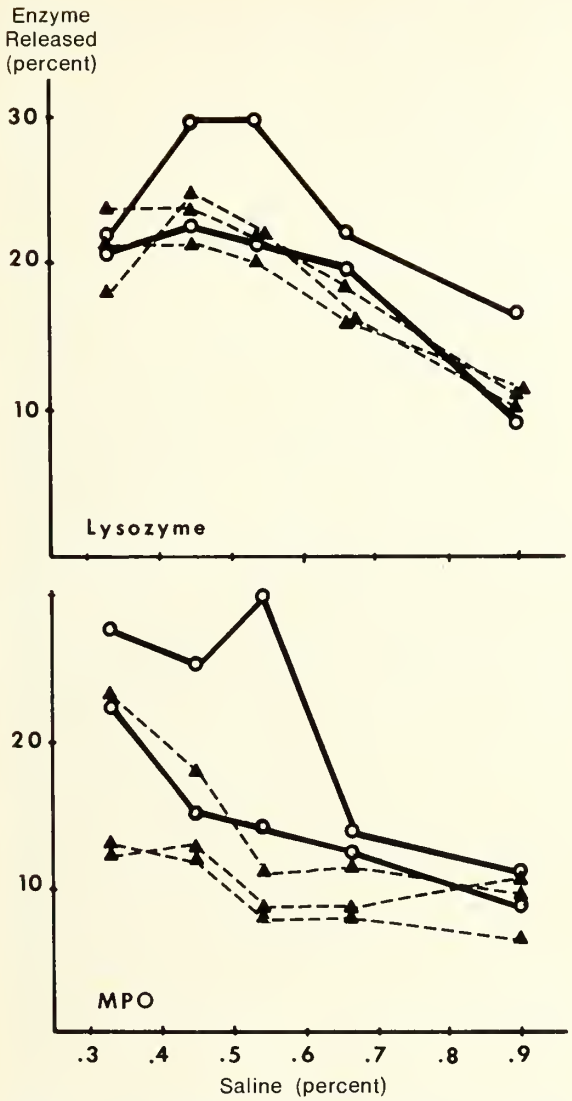

Figure 1.—Percentage of enzyme—lysozyme or myeloperoxidase (MPO)—released at osmotic concentrations ranging from 0.3 to 0.9 percent saline. Circles: Familial Mediterranean fever (FMF) cells; triangles: control cells.

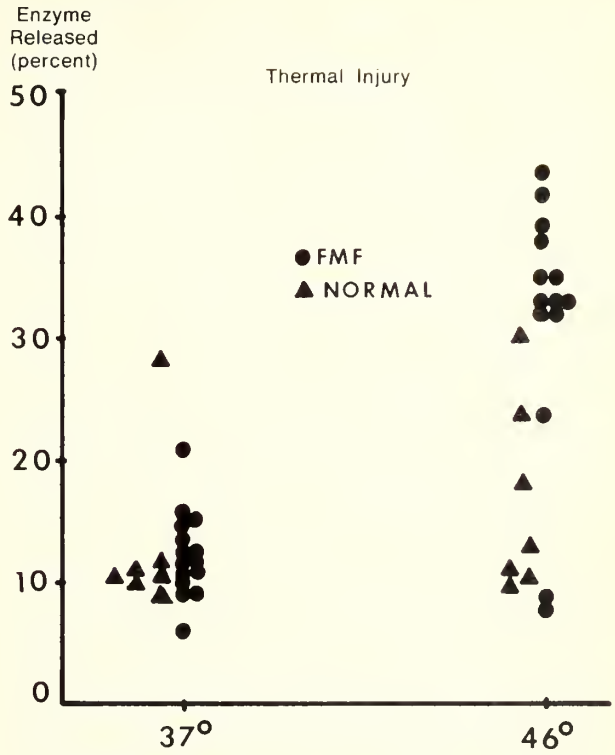

Figure 2.—Percentage of lysozyme released from familial Mediterranean fever and normal cells at 37°C and at 46°C.

gest Candida organisms. No difference between the FMF and control cells has been observed in their lysozyme release after pH changes, phagocytic or traumatic stresses. Preliminary studies suggest some increase in lysozyme and myeloperoxidase release in FMF cells over control cells exposed to low osmotic concentrations (Figure 1). At 0.54 percent sodium chloride, control cells released 20 to 22 percent of their lysozyme and 8 to 11 percent of their myeloperoxidase, whereas FMF cells released 21 to 30 percent of their lysozyme and 14 to 30 percent of their myeloperoxidase. More studies need to be done before the significance of these differences can be evaluated. Familial Mediterranean fever cells also seem to release more lysozyme in response to high temperature (46°C). The release of lysozyme activity ($P<0.01$) is greater in FMF cells (mean 33 percent, ±8) than in control cells (mean 19 percent, ±8) (Figure 2). This release of lysozyme is slightly decreased (29 percent, ±5) in patients receiving colchicine. Some ethnic variability may also be present in patients with familial Mediterranean fever. In afflicted Jews, lysozyme release was 25 percent (±10), whereas in Armenians it was 35 percent (±6). In one of the Jewish patients, studies were done at various phases of disease; although there was no increase in lysozyme release during the asymptomatic periods, there was an increase in thermal lysozyme release during an acute attack (Figure 3).

The significance of the increased lysozyme release at high temperatures and possibly at low osmotic concentrations, is uncertain. We have been unable to identify a difference in the cell population or the stability of lysozyme in the patients with familial Mediterranean fever to account for this difference. It is not certain at this point whether the lysozyme we measure is the result of cell death (with release of all the cellular con-

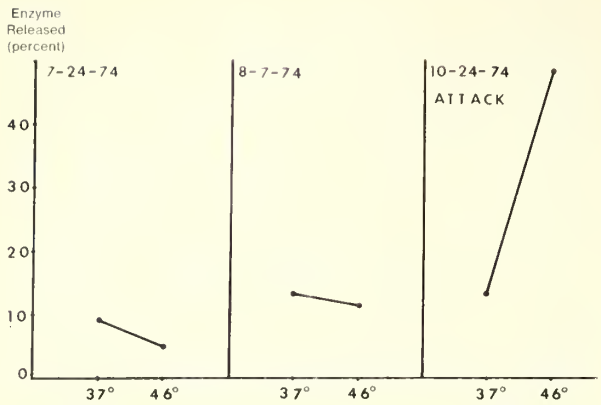

Figure 3.—Percentage of lysozyme released at 37°C and at 46°C in a patient with familial Mediterranean fever, measured during two asymptomatic periods and an acute attack.

tents), a consequence of reverse endocytosis (with extracellular discharge of granular enzyme) or a result of leakage of undischarged granules. This pattern of lysozyme release may be a general characteristic of inflammatory reactions, therefore other febrile diseases need to be investigated. If this is a characteristic unique to familial Mediterranean fever, it suggests that the phagocytic leukocyte may play some part in the pathogenesis of this disease. Although these preliminary data may suggest a possible role of the leukocyte, further studies are needed to elucidate the contribution of this cell to the pathogenesis of familial Mediterranean fever.

Metabolic Effects of Colchicine

JAMES R. KLINENBERG, MD*

COLCHICINE, an extract of the colchicum autumnale plant, was introduced for the treatment of acute gout in the sixth century, AD, and has been in continuous use for this purpose in prescribed form for more than 200 years. Despite its ancient lineage, there are still many unresolved questions about the clinical value of colchicine, its metabolism and its mechanism of action. In addition to its use in gout, colchicine was tried in many other acute inflammatory conditions, such as rheumatoid arthritis, and during the acute attacks of familial Mediterranean fever, without much success.[4,5] However, if given prophylactically, the drug has been found effective in preventing or reducing the frequency of familial Mediterranean fever attacks.[15-18]

The mechanism of the action of colchicine is still under extensive study; most of the information has been gathered from studies relative to its action in acute gouty arthritis. Colchicine is an anti-inflammatory agent, although a weak one in clinically tolerated doses. Its action may depend on interference with a number of steps in the inflammatory reaction. The anti-inflammatory and antimitotic effects of colchicine may depend upon the same biophysical mode of action.

The model for the action of colchicine is crystal-induced inflammation, that is, acute gout. Microcrystals of sodium urate (0.5 to 8 micra) are ingested by polymorphonuclear leukocytes that appear in synovial fluid, either by random locomotion or in response to a chemotactic factor. The neutrophils ingest urate crystals and during the process several biochemical reactions occur, such as mobilization and release of lysosomal enzymes, and activation of vasoactive polypeptides. These reactions induce local conditions that may favor more urate deposition, ultimately resulting in a vicious cycle. In acute gout, colchicine is most effective when given either early in the attack or prophylactically. It has no effect on the serum urate, the urate solubility or on the crystals per se, but acts primarily on the inflammatory reaction. Pretreatment with colchicine diminishes urate-induced inflammation in both skin and joints. The effect of colchicine on inflammation is not limited to urate crystals; similar effects have been shown with sodium orotate crystals and certain bacteria, such as Staphylococcus aureus.

Why does a weak anti-inflammatory agent, namely colchicine, have such a potent effect in acute gout? This may relate to certain peculiarities of the acute gouty inflammation: its complete reversibility (showing that the inflammatory trigger is not persistent) and a pronounced sensitivity to the drug by the predominant inflammatory cell in the synovial fluid, the polymorphonuclear leukocyte.

Inflammatory conditions in which colchicine may be clinically useful in man include acute gout, sarcoid arthritis, recurrent acute arthritis associated with chronic renal failure and hemodialysis, calcific tendinitis resembling gout, familial Mediterranean fever and, possibly, renal

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amyloidosis. Common features of the above conditions include sensitive target cells and intermittent and variable inflammatory triggers.

The effect of colchicine on polymorphonuclear leukocytes has been extensively studied. Colchicine suppresses some biochemical functions associated with phagocytosis; it also interferes with lysosomal degranulation and phagolysosome formation. Consequently, by inhibiting the fusion of the lysosome and phagosome, colchicine suppresses the specific release of granular enzymes from human polymorphonuclear leukocytes. It may inhibit uptake of one particle but not another; for example, colchicine suppresses the uptake of starch, Pseudomonas and urate, but not of Staphylococcus or Candida albicans under all conditions. Colchicine suppresses the generation of chemotactic factors that are induced by the phagocytosis of urate crystals by polymorphonuclear leukocytes. Colchicine interferes with the granulocyte-kallikrein system, which promotes the generation of kinins. It also inhibits the random motility of the human neutrophils and their adhesion to glass beads, and therefore, possibly to vascular endothelium as well.

The above effects occur mainly in *in vitro* systems and at varying concentrations of colchicine. In man, after administration of 2 mg of colchicine intravenously the mean zero time concentration of serum colchicine is 5×10^{-8} molar; after 3 mg of colchicine, the mean leukocyte concentration is approximately ten times greater, that is, 5×10^{-7} molar. Colchicine may affect the neutrophil *in vivo* at a number of different points. Margination, random locomotion, chemotaxis, and functions associated with phagocytosis are known to be related to inflammation; all are affected by colchicine *in vivo*.

Malawista[12] has studied extensively the relationship of the anti-inflammatory and antimitotic effects of colchicine. He has suggested that there is a common mechanism to explain the actions of colchicine as an anti-inflammatory and antimitotic agent, that is, interference in cells with the organization of the labile fibular systems concerned with structure and movement of the microtubular system. Colchicine stops cells from dividing by interfering with the mitotic spindle, a protoplasmic gel that forms at metaphase and without which the chromosomes cannot separate properly. This spindle can be shown by electron microscopy to contain arrays of microtubular elements that decrease in number and length and may even disappear after colchicine treatment. Spindle microtubules are in dynamic equilibrium with disorganized protein subunits; colchicine binds these subunits and keeps them from polymerizing into microtubules. Therefore, Malawista has evidence to support the theory that colchicine binds to protein subunits and thereby prevents microtubule function. Without microtubules the lysosomes and phagosomes cannot merge and there is inhibition of degranulation in the neutrophil.

Since the microtubular system is ubiquitous in cells, the potential effects of colchicine in man may be limited only by the number of cell systems to which the drug has access. Other cell systems (in which this mechanism may prevail) could include histamine release from rat peritoneal cells, macrophages, synovial lining cells and the vascular endothelium.

Some similarities between acute gout and familial Mediterranean fever have been suggested; both are manifested by acute inflammation. The theories regarding colchicine's mode of action in urate crystal-induced synovitis have already been discussed. What about the mode of action in familial Mediterranean fever? Goldfinger[15] noted that the synovium from patients with familial Mediterranean fever showed acute inflammation, and that the synovial effusion from one such patient contained polymorphonuclear leukocytes showing notable phagocytic activity and spherical inclusion bodies. Therefore, interference with phagocytosis, both in gout and familial Mediterranean fever, could break the inflammatory cycle at its inception with resultant protection from clinical sequelae.

Colchicine Prophylaxis in Familial Mediterranean Fever

ROBERT S. PETERS, MD*

THE USE OF DRUGS for suppression of the febrile paroxysms of familial Mediterranean fever had been unsuccessful until 1972, when Goldfinger[15] reported a pronounced reduction in the frequency of attacks in five patients receiving chronic colchicine therapy. Subsequently, results of three double-blind, controlled studies[16-18] confirmed the ef-

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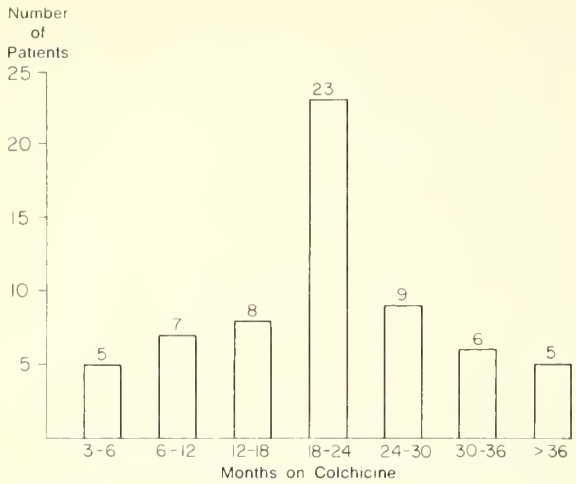

Figure 4.—Duration of chronic colchicine therapy in 63 patients with familial Mediterranean fever.

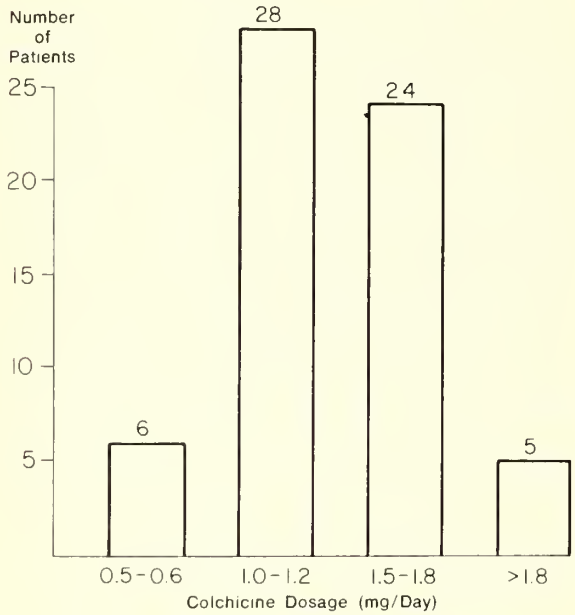

Figure 5.—Daily dosage of colchicine administered. (Each tablet contains either 0.5 or 0.6 mg of colchicine.)

ficacy of colchicine in preventing or reducing the frequency of attacks.

At UCLA, daily colchicine therapy has been used in 63 patients who were severely handicapped by the severity or the frequency of their attacks, or both. Of these 63 patients, 51 have been treated for one or more years, 20 for at least two years, and 3 for more than seven years (Figure 4). Initially, most patients received 1.0 to 1.2 mg (two tablets) of colchicine per day; children under 15 and a few adults, 0.5 to 0.6 mg (one tablet) per day as a start. In approximately 50

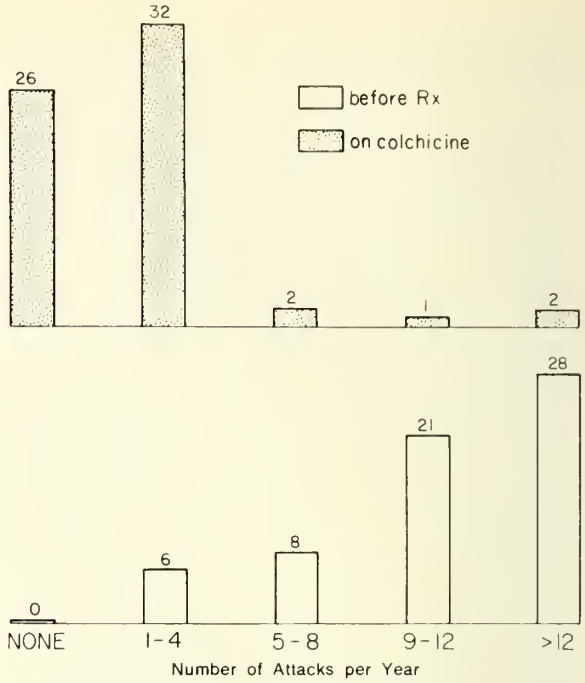

Figure 6.—Comparison of attack frequency before and during colchicine therapy.

percent of patients receiving these low doses, attacks continued to occur and the dosage was increased to three tablets a day. In five patients, dosage higher than 1.8 mg daily was attempted but proved to be successful in only three. The daily colchicine dosage ultimately administered is shown in Figure 5.

In patients receiving 1.8 mg of colchicine a day or less, diarrhea has usually been very mild and transient. In three patients, however, diarrhea persisted at significant severity, necessitating reduction of dosage from 1.8 mg to 1.2 mg per day. In four patients, brief courses of antispasmodics were required for mild but persistent diarrhea or abdominal cramps.

The results of prophylactic colchicine therapy are shown in Figure 6. In 26 patients attacks of familial Mediterranean fever ceased for periods ranging from 3 to 36 months, the mean duration being 13.3 months. In 32 patients receiving colchicine only one to four attacks occurred per year (mean 1.9 attacks per year). This is in contrast with the pretreatment attack rate of 3 to 40 (mean 21.5) attacks per year. Eight cases were considered treatment failures: one patient who discontinued the medication because of nausea, and seven patients who had either no appreciable reduction in attack frequency or who had five or more attacks per year. In two of the patients with

no significant reduction in attack frequency, significant psychiatric disturbances existed, and in one, narcotic dependence was later identified and treated. Using each patient as his own control, there seems to be a 70 percent (or greater) reduction in the frequency of attacks in 55 patients (87 percent). However, spontaneous remissions lasting several months are known to occur in this disease, and may be reflected in some of the apparently favorable results. The optimal effective dose of colchicine seems to be 1.5 to 1.8 mg per day.

Initially, because of the youth of many of the patients and the duration of the therapy, there were concerns about chromosomal nondysjunction and azoospermia. There was, however, no evidence to support this concern. Recently, the Tel Hashomer group in Israel[19] reported the use of prophylactic colchicine in 350 patients with familial Mediterranean fever; 84 of these patients were treated for at least one to three years. These studies showed again the effectiveness of treatment in adults and children, the latter requiring adult doses of colchicine. There was no effect on reproduction or on the progeny in 11 pregnancies, three male patients fathering normal children. Of 13 patients with amyloid nephropathy, proteinuria was significantly diminished in six patients. Proteinuria did not increase in any patient, nor did it appear in any patient who did not have it at the beginning of prophylactic colchicine therapy. Colchicine therefore appears to be clearly established as the drug of choice in the management of familial Mediterranean fever.

DR. SCHWABE: *There is little doubt that progress has been made in recent years in our understanding of familial Mediterranean fever. The clinical manifestations have been clearly defined, patterns of inheritance have been described, differences in the prognosis of various ethnic groups have emerged and unproven methods of treatment have been eliminated. It seems that colchicine prophylaxis is effective in most patients, but we do not know the precise reason for this effect, nor whether this drug will prevent the development of amyloidosis in those groups at risk.*

The cause of familial Mediterranean fever is still a matter of intense speculation. The recurrent febrile paroxysms have suggested that at various times there is a release of a material capable of inducing both fever and serosal inflammation, but the nature of this pyrogen is still unknown. Is it an intracellular enzyme released from leukocytes or from other tissues? Why do some patients go into remission during pregnancy, and why do some get attacks just before their menstrual periods? Could the cause be a pyrogenic hormone, as has been suggested? These and other questions remain to be answered and require more research before the precise nature of this fascinating disease can be clarified.

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Refer to: The pickwickian syndrome—Medical Staff Conference, University of California, San Francisco. West J Med 127:24-31, Jul 1977

The Pickwickian Syndrome

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *At Medical Grand Rounds this morning we are going to have an interesting and important topic related to respiratory difficulties, the pickwickian syndrome. The case presentation will be given by Dr. Homer Boushey, who will also lead the discussion.*

DR. BOUSHEY:† The major problem of today's patient is one of daytime somnolence. The patient is a 35-year-old unemployed cab driver who presented with a two-year history of repeatedly falling asleep throughout the day. The somnolence occurred at any time—while watching television, conversing with another person or playing with his children. He had twice fallen asleep while driving his car and had once driven his car into a ditch. On one occasion he alarmed a passenger by driving his cab several blocks on a downtown street, acting as if he were "in a trance." One consequence of these events was the suspension of his driver's license, depriving him of his means of support. During the same two years, the patient had difficulties with sleeping at night. He slept with great difficulty, often waking with a gagging sensation, feeling as though "a valve had been turned" in his throat so that he rose from the bed fighting for air. His wife reported that he snored loudly and thrashed about in bed, twice striking her in his sleep. She had taken to retiring on the couch in self-defense. The patient said that there had been no hallucinations, cataplexy, sleep walking or urinary incontinence. One year before referral here he was admitted to hospital for massive edema of both legs, extending from the ankles to the thighs. Findings on a radiograph of the chest, electrocardiogram, electroencephalogram, and CT brain scan showed no abnormalities. He was treated with hydrochlorothiazide and methylphenidate hydrochloride USP (Ritalin®), in doses from 10 to 40 mg three times a day. The leg edema cleared, but somnolence did not improve and the patient was referred here for further evaluation.

Additional history was obtained, some of it from his mother. The patient's birth weight was 12 pounds. He was the biggest of eight siblings. His mother recalled that he had heavy breathing as a child, and that she twice asked a physician about its significance. She was reassured that it was unimportant. She specifically did not recall episodes in which she was alarmed that her baby

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†Homer Boushey, MD, Assistant Professor of Medicine.

had stopped breathing. The patient's development was slow. He did not walk until the age of three, and pubescent changes appeared later than in his brothers. At the age of 16 he weighed 265 pounds and played defensive tackle on the high school football team. Three years before admission his weight was 300 pounds; two years before admission, at the onset of his difficulties with sleep and with somnolence, his weight was 385 pounds. At the time of referral it was 418 pounds.

The patient's social history is remarkable for a long history of difficulty with authority. He ran away from home at the age of 12 and reports that he has since had 157 felony arrests and has spent nine years in penal institutions. He is the only one of his siblings to have been arrested or incarcerated. He married three years ago and has three stepchildren. He has had no further difficulty with the police, and has been gainfully employed until the recent loss of his driver's license.

On physical examination he presented as a massive, well-muscled man who fell asleep twice during the examination, but who conversed lucidly while awake. Vital signs included a blood pressure of 140/80 mm of mercury, pulse 78, respiratory rate 18 and regular. He was afebrile. He had no papilledema; the tonsils were absent. No abnormal tissue was noted in the posterior pharyngeal wall. Indirect laryngoscopy showed no abnormalities. He had a short, thick neck; the thyroid was not enlarged or nodular. The findings on examination of the chest were remarkable only for the presence of distant breath sounds. There was no distention of the jugular venous pulse. The point of maximal cardiac impulse was not palpable. Heart tones were distant. The abdomen was remarkable only for immense girth. Extremities showed 1 to 2+ ankle edema. General neurological examination was within normal limits.

Laboratory data showed normal values for hemoglobin, hematocrit and leukocyte count. Results of blood studies were remarkable only for a bicarbonate value of 33 mEq per liter. No abnormalities were noted on an electrocardiogram, an x-ray study of the chest and thyroid studies. An echocardiogram was difficult to interpret because of the thickness of the chest wall, but was thought consistent with slight right ventricular hypertrophy. Pulmonary function tests (Table 1) were done with difficulty. The patient fell asleep in the body plethysmograph, while breathing on the spirometer and at other times. The studies showed reduced lung volumes and vital capacity. Measurements of maximal expiratory flow were normal. There was very slight maldistribution of inspired air and airway resistance was normal. Despite this normal appearance of awake pulmonary function, arterial blood gases were abnormal: oxygen pressure (Po_2) equaled 45, carbon dioxide pressure (Pco_2) equaled 50, pH equaled 7.38. In summary, this patient with a lifelong history of obesity presented with daytime somnolence, difficulty with sleep at night, and laboratory studies showing hypoxemia and hypercapnea despite normal values for screening pulmonary function studies while awake.

The association of obesity, somnolence and polycythemia has been described in the medical literature for 150 years, but the association was not given the name of pickwickian syndrome until 1956 by Burwell, Robin and co-workers.[1] They defined the major features of the syndrome

TABLE 1.—*Findings on Screening Pulmonary Function Studies*

Results	*Predicted*	*Observed*	*Percent Predicted*
Vital Capacity (liters):	5.5	4.0	72
Expiratory Reserve Volume (liters):	1.8	0.3	15
Residual Volume (liters):	2.2	2.0	91
Total Lung Capacity (liters):	7.7	6.0	77
Residual Volume/Total Lung Capacity (percent):	28.0	34.0	
Pulmonary Diffusing Capacity: (ml/minute per mm of mercury)	34.4	39.6	119
Forced Expired Volume, 1 second (liters):	4.4	2.8	
Percent expired in 1 second:	80.0	83.0	
Single Breath Distribution (percent):	2.0	2.2	
Airway Resistance (cm of water/liters per second)	1.0 - 2.8	2.25	

Arterial Blood Gases: Po_2 45 mm, Pco_2 50 mm, Ph 7.38; Base excess +3.2 mEq/L
Clinical Diagnosis: Narcolepsy vs. Pickwickian Syndrome
Sex: M, Age: 32, Ht: 185 cm., Wt: 189 kg., Hb: 13.6 gm/dl

TABLE 2.—*Clinical Features of the Pickwickian Syndrome**

1. Obesity, pronounced
2. Somnolence
3. Twitching
4. Cyanosis
5. Periodic respiration
6. Polycythemia, secondary
7. Right ventricular hypertrophy
8. Right ventricular failure

*From Burwell CS, Robin ED, Whaley RD, et al: Am J Med 21:811, Nov 1956[1]

(Table 2). They suggested that this association be named the pickwickian syndrome because they resembled the description of Joe, the fat boy, in Charles Dickens' book *The Posthumous Papers of the Pickwick Club,* commonly called the "Pickwick Papers." Dr. Comroe objects to this designation on both literary and scientific grounds.[2] First, he points out that Joe was neither a member of Mr. Charles Pickwick's family nor a member of his club; he was simply not a Pickwickian. If the features of the pickwickian syndrome did describe the members of the club, we should imagine their meetings much like those of the ad hoc subcommittee on the teaching of nutrition on the undergraduate curriculum, a collection of well-fed people sleeping quietly after a delicious lunch at the faculty club. Dr. Comroe's scientific objections are that Joe, the fat boy, is never described to be cyanotic, apneic or suffering from alveolar hypoventilation. Dr. Comroe goes on to note that the syndrome is simply misleading, as it was in this case. Fat people can suffer from somnolence and from life-threatening disturbances in respiratory function and yet not meet the criteria described. Today's patient, for example, was not polycythemic. At times in this hospital stay, his arterial P_{CO_2} was normal, showing that he did not hypoventilate at all times. If he had been tested at only one point when awake and stimulated, the diagnosis could easily have been overlooked.

In the remainder of my discussion, I hope to review several aspects of this engrossing subject. How does obesity affect the mechanics of breathing? Why do some but not all obese patients hypoventilate? Why are some but not all patients somnolent? I would like to raise further questions about the causes of the syndrome and to share some speculations about the problems faced by this patient in particular. The most obvious fact about obese people may be the most important: they have an immense additional amount of tissue to move. In inspiration, the respiratory musculature not only faces the weight of the additional tissue on the chest wall but must also displace the abdominal wall outwards to permit the downward movement of the diaphragm. In obesity the compliance of the chest wall, by which one really means the chest and abdominal wall, is reduced. Two very important effects result from this decrease in chest wall compliance. The first is that the work of breathing is greater. It simply requires more work to move the chest in and out. The second effect is to reduce the volume of lungs at the end of inspiration (functional residual capacity), the rest point at which the patient is making no inspiratory or expiratory effort (Figures 1A and 1B). The reduction in functional residual capacity is the most consistent abnormality found in pulmonary function tests of obese patients. A second way of looking at this, as shown in Figure 2, is by examining the flow volume curve, a familiar test of pulmonary function. At lower lung volumes, where obese patients normally breathe, the cross-sectional diameter of the airways is smaller than at high lung volumes, due to the lower values for lung recoil pressure. In the patient under discussion, the functional residual capacity was virtually superimposed on the residual volume. This has two important consequences. The first is that he breathes at a point where the airways are not so distended—their diameter is smaller. Therefore, not only must he do an increased amount of work to move the chest wall, he must also do more work to overcome the resistance to air flow in these narrowed airways, further increasing the already great work of breathing. The second point is that at residual volume the air inspired is distributed predominately to the middle and upper lung zones. Perfusion is distributed primarily to the lower and middle lung zones. Normally, when one breathes at a higher lung volume, as a nonobese person does, ventilation is distributed to the same areas where perfusion goes. As a result of obesity then, a person breathes at a lower lung volume and ventilation goes to areas which are poorly perfused, the well-perfused bases receive less air. Arterial hypoxemia results.

In summary, the mechanics of breathing are largely affected by the decrease in chest wall compliance. The work of breathing is increased and the functional residual capacity is decreased. Gas exchange shows hypoxemia due to mismatching of ventilation and perfusion of the lung bases.

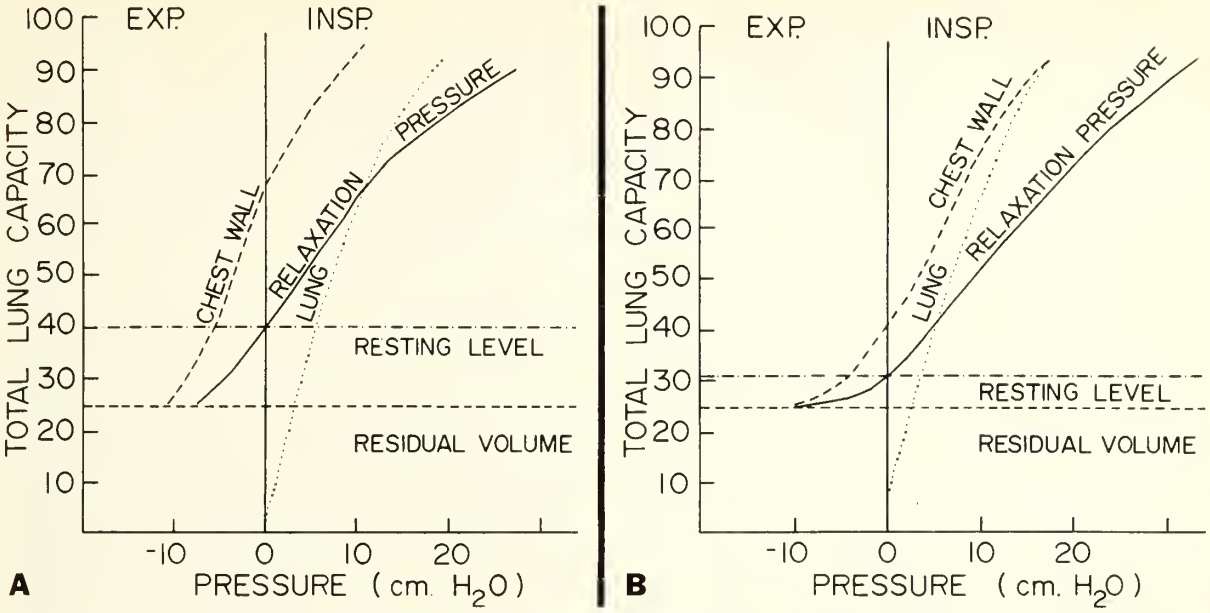

Figure 1.—**A**, Determinants of function residual capacity. The volume of the lung when the subject makes no inspiratory or expiratory effort (pressure = 0) is set by the opposing effects of the chest wall and the lung, **B** shows the reduction in functional residual capacity (FRC) resulting from a decrease in chest wall compliance. (Figure 1A is from Rahn H, Otis AB, et al: The pressure-volume diagram of the thorax and lung. Am J Physiol 146:161, 1946)

There are several theories as to why some obese patients are hypercapneic. One theory is that patients are hypercapneic because the work of breathing is so great. Another theory is that they have relative weakness of the respiratory muscles. A third theory is that the mechanisms controlling ventilation are altered, so their sensitivity to carbon dioxide and to oxygen is abnormal.

The great increase in the work of breathing is shown by the rise in oxygen consumption produced by voluntary hyperventilation. Normally, one can achieve a seven-fold increase in minute ventilation with a small increase in oxygen consumption. Patients who have congestive heart failure, emphysema or obesity can achieve an increase in minute ventilation only at the price of a great increase in oxygen consumption because the work of breathing is so great.[3] To avoid the high energy cost of such work, the central "thermostat" which sets the arterial P_{CO_2} may be readjusted to a higher level. This theory argues that one has alveolar hypoventilation to avoid the high work of breathing. The problem with the theory is that it does not explain why some people who are fat hypoventilate and others, equally fat, do not.

Rochester and Enson[4] speculate that hypoventilation results not simply from the increase in the work of breathing but from a combined increase in the work of breathing and weakness of

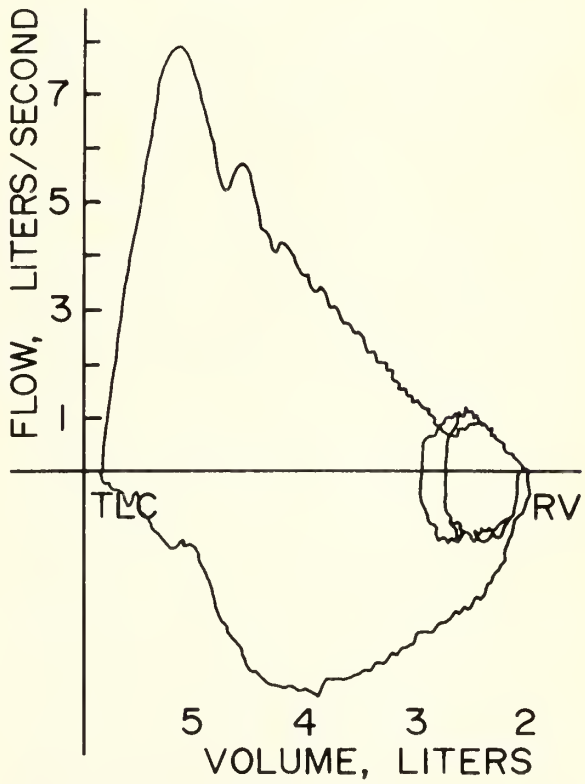

Figure 2.—The flow-volume curve. The outer envelope shows the maximal inspiratory and expiratory flow rates (vertical axis, expiration upward) plotted against lung volume (horizontal axis). Tidal breathing is seen to occur at low lung volumes, so that functional residual capacity is superimposed on residual volume (RV). TLC = total lung capacity.

the respiratory muscles. They support this contention with few data, but it does suggest that patients who are obese and hypoventilate can generate smaller maximal inspiratory pressures than normal, and can achieve less than normal maximal voluntary ventilation.

We investigated this latter possibility in the patient under discussion first by taking a careful history. While last incarcerated in prison he occupied his recreational time practicing weight lifting. At one time he could clean-snatch 475 pounds. This is 50 pounds short of the world's record, but probably puts him in at least the normal range for muscle strength. His measured maximal inspiratory pressure was 93 cm of water, in the middle of the normal range for his age. We did not test how this relates to the massive impedance imposed by the chest wall. So his muscle strength was normal, but it is true that his work of breathing was greatly increased.

Another theory to explain why obese patients hypoventilate is that some have a diminished sensitivity to low oxygen or to elevated carbon dioxide tensions. In the normal population the response to carbon dioxide varies greatly. Some people of normal habitus and without lung disease are relatively insensitive to carbon dioxide. They increase minute ventilation very little with an increase in arterial carbon dioxide (CO_2). The theory is that if these people acquire a disease which increases their work of breathing—either obstructive lung disease or obesity—alveolar hypoventilation is apt to develop. There are some problems with this theory. Some patients with the obesity-hypoventilation syndrome have been reported to have normal CO_2 sensitivity. Furthermore, patients with the syndrome who are insensitive to CO_2 are found to have a normal response to CO_2 after they have lost weight. We have no way of directly measuring the neural output from the respiratory center. Ventilation is a function of the efficiency of the entire respiratory system in response to a given neural output. Other investigators have argued that the hypoventilation is not due to insensitivity to carbon dioxide, but to an insensitivity to low oxygen levels.[5]

Dr Severinghaus' laboratory carried out tests of the response to hypoxemia and hypercapnea in our patient. Our patient's response to carbon dioxide was about 48 percent of normal, a modest diminution in CO_2 sensitivity. The increase in ventilation on reducing the P_{O_2} from 150 to 40 is in the normal range. We believe that the patient may have a slight insensitivity to carbon dioxide but has a normal response to hypoxemia.

The causes of hypercapnea are somewhat unclear, but more satisfying explanations can be offered for the daytime somnolence of these patients. The somnolence is not a function of arterial P_{CO_2}; patients with obstructive lung disease who have equally high arterial P_{CO_2} are not somnolent. The secret of the somnolence was discovered by Gastaut, who showed that patients with this syndrome fail to breathe normally at night.[6] Their sleep is frequently interrupted by apneic periods of at least two types. The first is central, in which the patient makes no effort to breathe, and the second is obstructive, in which the inspiratory effort moves no air because of an obstruction in the upper airway. In this latter case, what has probably happened is that the tongue falls against the posterior pharyngeal wall. Apnea occurs up to 300 or 400 times per night, and explains a great deal about the syndrome. The patient is awakened repeatedly throughout the night by the fall in P_{O_2} and rise in P_{CO_2} produced by the apneic periods. Throughout the day the patient is somnolent, trying to recover what has been denied to him throughout the night. Another consequence of recurrent apnea is failure of the right side of heart. The rise in P_{CO_2} and fall in P_{O_2} stimulate pulmonary vasoconstriction. As this occurs hundreds of times throughout the night, the mean load imposed on the right side of the heart is increased, and right heart failure may develop.

Our patient proved a very good example of the syndrome. The patient was observed in the intensive care unit overnight with an arterial catheter and esophageal balloon in place. A CO_2 probe was placed at the nose (Figures 3A and 3B). Shortly after falling asleep, the pattern of breathing was slightly irregular, but not remarkably so. Gas exchange was normal. Some hours later the pattern of breathing became remarkable. Periods of apnea of 14 seconds appeared, during which he made no attempt to breathe. Subsequent inspiratory efforts were of progressively greater magnitude, as he tried to move air against an obstructed airway. Finally, with a snore and with movement of the arms and legs, the patient resumed breathing, took two or three breaths and reentered an apneic period. This pattern went on throughout the night. Gas exchange became abnormal; hypoxia, hypercapnea and respiratory acidosis developed. During the apneic period, his pulse fell to as low as 44 beats per minute. When

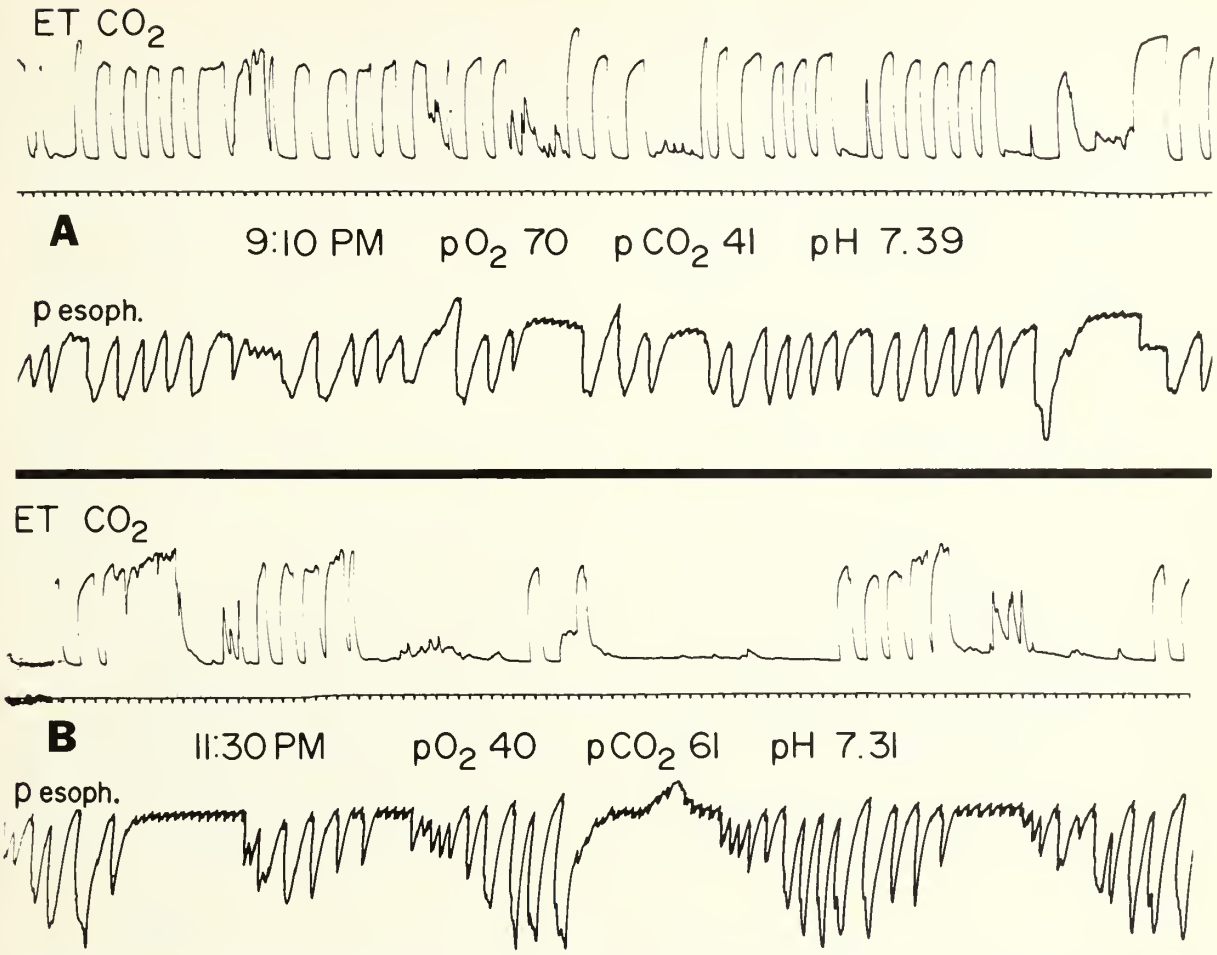

Figure 3.—Pattern of breathing during sleep. End-tidal carbon dioxide (CO_2) is measured by a probe placed at the nose, esophageal pressure by an esophageal balloon. **A** shows slight irregularities in the pattern of breathing, but gas exchange is normal. **B** shows periods in which neither end-tidal CO_2 nor esophageal pressure (P esoph.) changes, indicating that the patient has made no effort to breathe (central apnea; shown on far left of the tracing) and periods in which end-tidal CO_2 does not change despite increasingly great changes in esophageal pressure, indicating the presence of obstruction of the upper airway (obstructive apnea, shown in center and far right of tracing).

he resumed breathing the pulse rose and the blood pressure increased to 220/130 mm of mercury. A second sleep study was done on the following night when an electroencephalogram was also recorded during sleep. Again the patient's sleep was interrupted by recurrent apnea. He breathed for 10 seconds, was apneic for 30, breathed for 10, and so on. These studies supported a diagnosis of obesity, alveolar hypoventilation and sleep apnea.

The therapeutic options at this point were to induce weight loss, to try hormonal therapy, or to gain control of the upper airway. The patient stated that many attempts at dieting had been so unsuccessful that he was reluctant to try dieting again. An intestinal bypass operation, which has been done here in five similar patients with good response, was therefore considered. Another approach to therapy would be to treat the patient with progesterone. Progesterone has been shown to diminish alveolar hypoventilation and to diminish the daytime somnolence suffered by these patients,[7] but it has not been shown to abolish sleep apnea. The third possibility considered was to carry out a tracheostomy, bypassing the obstructed airway and immediately reversing the abnormal loss of sleep. The importance of prompt, effective therapy is shown by the high in-hospital mortality of the pickwickian syndrome, due to ventilatory failure, to arrhythmias associated with the change in blood gases in the apneic period and to pulmonary emboli.[8]

We discussed the options with the patient. He was very eager to go home for the weekend to

consider them, and we permitted him to do so. We reasoned that as he had his symptoms for two years it would be safe to let him go home for a brief period. While at home, however, apneic periods began to develop even while he was awake. Because he knew that the apneas were associated with sleep, he resolved to stay awake, taking up to 100 mg of Ritalin at a time in an attempt not to sleep, fearing that he would not wake up if he did so. He returned an exhausted, frightened and desperate man. An attempt to have him sleep with an endotracheal tube in place to bypass the upper airway obstruction was unsuccessful. On the following day, a tracheostomy was done. The change in the patient after the tracheostomy was striking. Somnolence disappeared within two days. He has been alert, personable and responsive. He also reported that he had resumed dreaming, something he could not recall doing since his early childhood. A repeat study of ventilation and electroencephalogram during sleep showed his respiration to be regular and uninterrupted. Analysis of an electroencephalogram showed sleep spindles, indicating deeper and possibly more restful sleep (Figure 4). These occurred only infrequently in the study done before tracheostomy. Blood gases were much better throughout the night, with Po_2, 56 mm; Pco_2, 52 mm, and pH, 7.40.

One might speculate that this patient's problem with sleep may have been a primary event, explaining both his obesity and his difficulties with authority throughout his lifetime. Dement reported that dream deprivation for one week caused many normal subjects to act paranoid, hostile or uncooperative.[9] In several subjects hyperphagia also developed, with gains in weight of from 3 to 5 pounds in one week of dream deprivation. This suggests that sleep deprivation may alter the satiety center, leading to hyperphagia and weight gain, and might also cause changes in personality, accounting for our patient's difficulty with legal authorities. There are obviously a myriad of determinants of personality, so this speculation is tendered with hesitation. The nursing staff on the ward, however, have been struck with the change in the patient after the tracheostomy was done, as he has suddenly developed a sense of humor and a greater tolerance of hospital routines.

Even if the speculation that this patient's personality was altered by sleep deprivation is too bold, it is clear that his somnolence and difficulty with sleep were related to abnormal breathing at

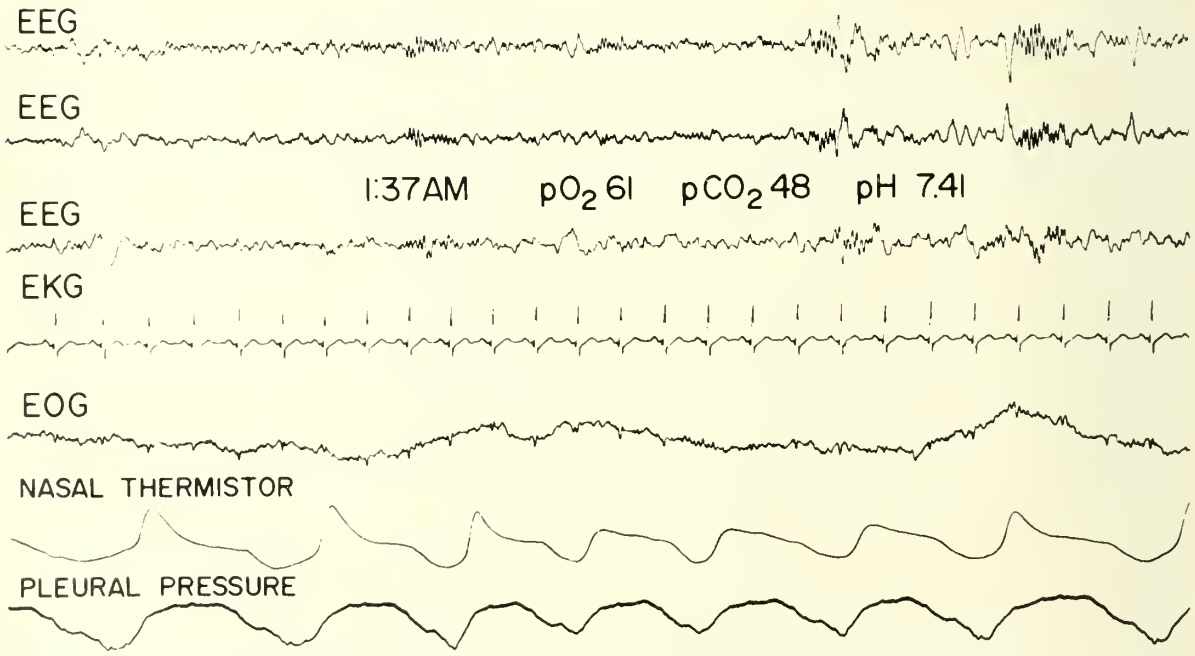

Figure 4.—Sleep study done after tracheostomy. From the top downward: upper three tracings show electroencephalographic activity (eea); EKG indicates the electrocardiogram; EOG indicates electromyogram of the extraocular muscles; the nasal thermistor indicates the temperature of air at the nose (inspiration with cooling of air, is downward; expiration upward); pleural pressure was measured from an esophageal balloon. Note the regular pattern of breathing and the presence of high frequency "sleep spindles" on the electroencephalographic tracings.

night. His case illustrates the limitations of examining a patient when awake: the cardinal abnormality was observed when he was asleep. As we have all learned so often, the practice of medicine does not end at sundown.

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Estrogens and Endometrial Cancer

DR. KISTNER: ". . . estrogens per se do not cause endometrial cancer in women. They may be related, but I don't think they cause it. There is no evidence that I know of that indicates estrogens are cell transformers. Estrogens do play a role in endometrial priming, which is really a permissive relationship. However, misuse of estrogenic substances may produce varying degrees of endometrial hyperplasia, which in certain unknown predisposed persons may lead to carcinoma of the endometrium, if continued stimulation by the estrogen is permitted.

"Now, if a physician elects to use estrogen for the correction of symptoms or signs of estrogen insufficiency, there are two therapeutic regimens available for the prevention of hyperplasia. The more popular and generally adopted method is the cyclic administration of the lowest effective dose for the shortest possible time with appropriate monitoring for endometrial cancer. The selection of the patient for estrogen therapy is most important. Obesity, hypertension, diabetes and infertility associated with oligoovulation are predisposing factors in the development of endometrial cancer and, therefore, in patients having this background endometrial biopsy or uterine aspiration should be done before the institution of therapy. Furthermore, annual endometrial sampling is recommended as long as estrogen is given. . . . Stated simply, then, the amount of estrogen given should ameliorate the signs and symptoms of estrogen insufficiency without producing bleeding or endometrial hyperplasia.

"The second regimen of estrogen administration takes advantage of the antiestrogenic effect of progestins. In this sequence, which I have not adopted, the estrogen is given constantly and the inevitable hyperplasia is averted by the intermittent use of potent progestins. However, the progestin must be given in adequate amounts, and monthly, in order to prevent the hyperplastic process from developing. This results in a withdrawal flow each month, an event that is undesirable to many postmenopausal women."

—ROBERT W. KISTNER, MD, *Boston*

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Important Advances in Clinical Medicine

Epitomes of Progress — Otolaryngology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in otolaryngology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in otolaryngology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Otolaryngology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Conservation of Hearing In Acoustic Neurilemmoma Excision

PRESERVING HEARING at acoustic neurilemmoma excision is an ultimate and logical extension of micro-oto-neurological surgery. Hearing conservation is an additional feature of the fundamental surgical goals of total tumor removal, preservation of life and VIIth nerve function. Both suboccipital and middle cranial fossa operative approaches have been described to save hearing in VIIIth nerve tumors. Recently the classic neurosurgical suboccipital approach coupled with micro-oto-surgical techniques has allowed total tumor removal with preservation of residual preoperative hearing in selected patients.

Several reasons can be given for conservation of hearing in acoustic neurilemmoma surgical operation: (1) The tumor may involve the only hearing ear. (2) Preoperatively the affected ear may have normal function. (3) Residual hearing in this ear postoperatively may give environmental sound awareness on the involved side. (4) The ability to locate the origin of sounds may be preserved. (5) The ability to understand in a noisy environment may exist if enough hearing is preserved in the ear in which the operation is done. The future functioning of the opposite ear is unknown. Presbycusis, sudden hearing loss or any of a number of other types of hearing deficit could develop.

The cases of ten patients with acoustic neurilemmoma and residual preoperative hearing were evaluated. Seven of the ten patients had some aspect of hearing preserved after microsurgical removal of the acoustic neurilemmoma. Three of the ten patients had von Recklinghausen's disease and in these hearing was lost. Of the seven patients who had some hearing preserved, four had more hearing loss postoperatively and three had postoperative thresholds equal to preoperative levels. Reviewing the opposite ear of the seven patients who had some hearing preserved postoperatively, all had normal functioning for speech. However, five had varying degrees of high frequency sensorineural loss in the ear that had no tumor. Eighteen months postoperatively, one patient with equal preoperative and postoperative hearing in the involved ear had progressive, sensorineural hearing loss bilaterally. This patient was functioning with a mild loss for speech in the ear not operated upon and with a moderately severe loss in the postoperative ear. Speech sound discrimination was good bilaterally, 92 percent

and 82 percent, respectively. The patient was fitted with a postauricular hearing aid for the postoperative ear and thereby obtained successful binaural hearing function.

Gentleness is extremely important to preserve cochlear function at removal of acoustic neurilemmomas. Gentleness is aided by microinstrumentation and surgical craft.

The chances of preserving hearing function at acoustic neurilemmoma excision increase with earlier diagnosis, surgical experience, better instrumentation and attempts at prevention of surgically induced vasospasm of the microvasculature to the cochlea.

MANSFIELD F. W. SMITH, MD

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Avoiding Mismanagement of a Paralyzed Face

THE PRINCIPLES of evaluation and care of a paralyzed face are not well known in the medical community, although the facial nerve is the most commonly paralyzed motor nerve. A paralyzed face has considerable emotional, physical and economic consequences for the patient. The observation of a prolonged total, slowly progressive or recurrent facial paralysis suggests neoplasm and mandates a careful diagnostic evaluation. In addition, trauma, infection and diabetes are common etiologic factors in seventh nerve paralysis. The art of prevention and management of problems of paralyzed faces has improved greatly during the past 15 years.

Clinicians should not be deceived that all facial palsies are Bell palsy (spontaneous idiopathic facial palsy) and that recovery will occur without incident. Careful evaluation and follow-up is always necessary. There are five findings related to facial motor function that tend to rule out Bell palsy:

(1) Simultaneous bilateral facial palsy.

(2) Recurrent unilateral facial palsy. In approximately 30 percent of cases tumors are present.

(3) Unilateral facial weakness which slowly progresses beyond three weeks. This is classically seen with neoplasm.

(4) Slowly progressive unilateral facial weakness associated with facial hyperkinesis.

(5) No return of facial function within six months following an abrupt onset of facial paralysis should strongly suggest a tumor.

Sparing of the forehead in facial paralysis has always suggested a central disorder. However, it is now well-established that the lesion may be peripheral. The orderly spacial arrangement of the facial nerve in the temporal bone can allow partial paralysis to occur.

Topographic diagnostic tests of the seventh nerve function should always be done on a patient with a paralyzed face that is complete, progressive or recurrent. Acoustic reflex studies, comparisons of lacrimal gland function and salivary gland function with the normal side, and taste and electrical tests help isolate the lesion. In addition, the adjacent eighth nerve function (both cochlear and vestibular) should be evaluated and radiographic studies of the temporal bone should be done.

Modern microsurgery has greatly improved the operative management of seventh nerve lesions and their sequelae. Care of paralyzed faces encompasses a host of dynamic and static procedures. Dynamic techniques include surgical removal of neoplasms, correction of traumatic defects, pressure, primary nerve suturing, nerve grafting, anatomic rerouting, seventh nerve crossover from the opposite uninvolved seventh nerve, seven nerve to twelve nerve anastomosis and nerve muscle pedicle grafts. There are now surgical techniques for repair of facial nerve defects intracranially in the internal auditory canal, within the temporal bone and external to the stylomastoid foramen in the soft tissues of the face. A primary seventh nerve repair including grafting is highly successful. Prolonged facial muscle viability may continue despite denervation and allows successful facial nerve repair years after the initial injury.

Static procedures involve (1) resection of redundant skin, (2) fascia lata strip suspension of the face and (3) weakening of the contralateral nonparalyzed musculature. In addition, certain adjunctive procedures complement the basic static and dynamic operations. These include (1) resection of a ptotic melolabial fold, (2) plication of parotid-masseteric fascia, (3) dermal graft suspension, (4) blepharoplasty, (5) brow lift, (6) canthoplasty, (7) horizontal shortening of the lower lid, (8) fascial suspension of the lower lid and (9) palpaebral spring.

Medical management includes care of the paralyzed orbit (half-moon-shaped paper tape fixed to the upper eyelid to stiffen and partially close the eye, used with glasses to prevent drying and frequent application of artificial tears), physiotherapy, and management of inflammatory and metabolic diseases including Bell palsy.

Counseling a patient with a paralyzed face is vital. A patient with facial palsy should be informed of the diagnosis, the type of lesion, etiologic factors and the significance of the results of the diagnostic tests. The patient also should be instructed carefully about management, expected timing of recovery, and the recommended sequence of medical and surgical procedures—including alternatives to them.

A patient with paralysis and distortion of a portion of his face must live with a severe social and functional handicap. The influence of gravity combined with the unopposed antagonistic pull of the opposite mimetic musculature of the face creates an extremely harsh bearing. Topographic testing to locate the site of the lesion of a paralyzed face is now well established. Modern microsurgical techniques used with dynamic and static procedures are highly successful for partial correction of paralyzed faces.

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Craniofacial Surgical Operation For Head and Neck Neoplasms

LARGE TUMORS of the head and neck generally are considered to be unresectable if they have become fixed to the base of the skull. For certain portions of this region this is very true; for example, excisions of the clivus must be limited to small peek holes because of the proximity of the pons and the certainty of sudden death if a major portion of this part of the sphenoid is removed. Thanks to the pioneering work of Lewis, Klopp, Smith and Ketchum, lesions of the head and neck that are fixed to the floors of the anterior and middle cranial fossae have become amenable to resection with a respectable chance of tumor ablation.

The ethmoidal and frontal sinuses and the nasal roof border on the anterior fossa. Spread occurs by extension through the posterior wall of the frontal sinus, or superiorly through the fovea ethmoidalis or the cribriform plate. The infratemporal fossa, the pterygomaxillary space, the sphenoid sinus and the temporal bone are adjacent to the floor of the middle fossa. Lesions of the nasopharynx, maxillary sinuses and nasal cavities may spread directly to these areas and thereby gain access to this part of the cranial cavity.

The most common benign lesion that may extend into the cranial cavity in this fashion is the juvenile nasopharyngeal angiofibroma. Its usual mode of intracranial extension is via the infratemporal fossa, through the greater wing of the sphenoid into the middle fossa. It may exert pressure on the orbital apex causing proptosis. Transfacial excision of such a lesion carries high mortality because of the difficulty in controlling extradural hemorrhage from the tumor vessels supplied by the internal carotid system. This supply is confirmed by angiography.

Carcinoma of the paranasal sinuses spreading to the cranial cavity by erosion through the floor of the anterior cranial fossa may fix to dura or invade the frontal lobes. Tomography in the Caldwell position usually shows the site and extent of this bone erosion. Tumors of the ear, such as glomus jugulare tumor and squamous and basal cell carcinoma, have been successfully treated using a combined approach since the early work of Campbell. Temporal bone polytomography and computerized axial tomography have greatly improved the assessment of extension of these tumors.

Craniofacial operations require the close cooperation of a neurosurgeon and otolaryngologist. Tumors that involve the anterior fossa and anterior reaches of the middle fossa are reached through a frontal and anterolateral craniotomy, respectively. A coronal or anterolateral scalp incision is made and a sterile towel covered with an antibiotic-soaked sponge is sutured to the base of the flap. This isolates the intracranial from the transfacial part of the operation. After a cranial bone flap has been removed the tumor is exposed from above and any involvement of dura or brain is excised. The dura is repaired with a fascia graft. The transfacial portion is dissected free and then with the neurosurgeon working from above, the tumor is delivered through the facial incision. The cavity is skin grafted and any cerebrospinal fluid that was removed earlier in the procedure is injected into the ventricular system to help fill out

the intracranial volume and prevent the formation of dead space between dura and cranium.

Of Ketchum's series in roughly a third of the patients no complications occurred, in another third there were minor complications and in the remaining third there were major life-threatening complications requiring intensive care and prolonged hospital stays. Most of the major complications occurred in patients who had received preoperative radiation treatment. This is similar to our own experience. Remembering that malignant lesions and benign tumors such as nasopharyngeal angiofibromas with intracranial extension were considered by many to be unresectable and for the most part incurable, this high complication rate appears justifiable.

Our experience with excision of tumors such as angiofibromas, esthesioneuroblastoma and carcinoma of the maxillary and ethmoid sinuses supports this concept of combined intracranial-transfacial excision.

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Immunity in Head and Neck Malignancy

Prognosis

ALTHOUGH NOTED in epidermoid cancers at other sites (for example, breast, colon and lung) the correlation between impaired nonspecific immune response and survival is nowhere stronger than in tumors of the upper aerodigestive system. The ability to show topical sensitization to 2, 4 dinitrochlorobenzene (DNCB) on secondary challenge has proved thus far the most popular and reliable *in vivo* assessment of the integrity of T-lymphocyte (cellular immune) function, thought to bear the major responsibility for tumor immune response. Eilber, Morton and Ketcham, for example, investigated 120 patients with a broad spectrum of head and neck malignancy. Of patients with localized and operable disease, 64 percent were DNCB reactive; 89 percent of these patients remained free of disease at six months irrespective of treatment. On the other hand, 85 percent of patients with locally advanced or disseminated disease were nonreactive to initial sensitization; only one of this group was alive one year later. Furthermore, posttreatment testing showed that a continued positive, or conversion from negative to positive, response was associated with tumor control in all cases.

Therapy

Unlike assessment of prognosis, immunotherapy in head and neck epidermoid cancer has not yet been widely initiated. However, several important theoretical principles already have emerged from pilot clinical and laboratory investigations. First, the maximum response capacity of a healthy, unaided immune system will destroy between 100 million and 1 billion cells, a tumor load only approaching detectability by conventional means. Second, the immune response destroys all cells within its capacity, unlike radiation or chemotherapy—both of which effect only those cells which are cytokinetically or biochemically vulnerable. Finally, the immune response is thought to be ubiquitously effective, so that targeted cells residual at the primary site, in regional lymphatics or distant in the viscera are equally subject to destruction. All of these considerations lead one to conclude that the first application of immunotherapy to malignancies of the head and neck will be in conjunction with contemporary modalities when tumor load is lowest.

ROBERT C. BONE, MD

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Additional Help for the Hearing Impaired

ADVANCES IN hearing aid design as well as new techniques and philosophy in hearing aid fittings have increased the number of patients who can benefit from amplification.

A patient with a high frequency loss, even when the hearing below 2000 Hz is normal or near normal, may have a great deal of difficulty in noisy situations and in distinguishing between

many high-frequency consonants. In the past, these patients were considered poor or impossible candidates for hearing aids. Now, however, with more sophisticated design, compression circuitry, open mold and CROS—BI-CROS fittings (CROS stands for contralateral routing of signals) and greater understanding of the effects of tubing size on attenuation of the low and middle frequencies, many patients with high-frequency loss can be fitted comfortably and necessary amplification achieved.

A patient with a unilateral loss was not, in the past, considered a candidate for amplification. However, because such a patient is unable to locate the origin of sounds, unable to hear someone on his "bad side" and finds communication in noise exceptionally difficult, he should benefit from binaural hearing. Therefore, depending on the needs, goals and motivation of these patients, a hearing aid may be of great value.

A child with a minimal hearing loss, even as little as 15 to 20 decibels, should not be overlooked as a possible candidate for amplification. The auditory channel is so important to the acquisition of communication skills that no child should be without adequate hearing for any period during his formative and educational years. A hearing aid should be worn on a trial basis and consultation among parents, physician, teacher and audiologist is essential before a decision is made.

JAMES A. CRABTREE, MD

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Bell Palsy—Update

THE PATHOGENESIS of idiopathic facial paralysis has been poorly understood for decades. Recent work indicates that a viral infection of the facial nerve is responsible. In many cases, a polyneuritis occurs, with viral involvement of the phrenic, hypoglossal, trigeminal, glossopharyngeal or other nerves. There is evidence that the responsible virus is herpes simplex.

The route of viral entry is thought by some investigators to be the oral cavity and submandibular gland, proximally via the chorda tympanic nerve, with subsequent involvement of the main trunk of the facial nerve. Clinically, this route is manifested by an early diminution in the submandibular gland's salivary flow rates, or by an erythematous chorda tympani as seen through the tympanic membrane. These changes frequently precede alterations in facial nerve function.

Therapeutically, controversy still rages over the efficacy of surgical decompression. Reports of immediate return of function following the operation tend to support the use of surgical procedures in selected cases. Recently, a well-controlled prospective study has challenged the rationale for steroid treatment in idiopathic paralysis.

ROGER CRUMLEY, MD

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The Brow Lift

A LOCAL BROW LIFT is a useful adjunctive procedure in cosmetic surgical procedures on the eyelids. Particularly benefical in elderly patients with brow ptosis, this procedure involves excising an ellipse of skin immediately above the hair of the brow. After primary closure the resulting upward and lateral slant of the eye yields a more alert and pleasing facial appearance. In addition, excess upper lid skin occasionally becomes functionally and cosmetically less disturbing.

A relatively simple operation, the local brow lift requires minimal undermining of skin margins and can be done readily under local anesthesia with little patient risk. The design of the surgical ellipse is dependent upon the location and extent of brow elevation desired. The resection is usually at the lateral aspect of the brow to maximize the upward lateral slant. A double layered closure with eversion of the skin edges is essential to minimize widening of the postoperative scar. "Tacking" sutures from the lower incision line to forehead periosteum has been ad-

vised by some authors and may be useful in preventing postoperative sagging.

An alternate approach to the local brow lift is an elliptical excision in the temporal hair line with undermining and elevation of forehead skin. This technique requires more dissection and is less accurate in the final brow positioning than is the local resection. One obvious disadvantage of a local brow lift is the visible scar that results. With proper suture technique and satisfactory use of cosmetics and eyebrow pencil for cover-up, however, this drawback is minimal.

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Local Anesthesia of the Ear by Iontophoresis

LOCAL ANESTHESIA of the ear canal and tympanic membrane by iontophoresis is an effective and painless procedure. In the past, the application of topical solutions to obtain anesthesia has been disappointing. Injections of local anesthetics have been painful, particuarly in children. Comeau and co-workers have revised Albrecht's method of iontophoresis so that it is an efficient means of anesthetizing the tympanic membrane for myringotomies and can be used for procedures involving the ear canal.

Iontophoresis is a process utilizing direct electrical current by which chemical agents such as epinephrine and lidocaine can be caused to migrate through intact skin. The ions in the anesthetic are positively charged and driven through the skin by the repelling action of the positive electrode (direct current). A fresh solution of 2 percent lidocaine (Xylocaine®) and 1:2000 epinephrine is used. Anesthesia of the tympanic membrane occurs in ten minutes.

The principal advantages of this technique are that the procedure is painless and much less bleeding occurs. The vertigo that occasionally occurs after Xylocaine® injection is avoided. This method of anesthesia is especially beneficial in myringotomies and in inserting collar-button tubes in children.

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Recurrent Laryngeal Nerve Section for Spastic Dysphonia

SPASTIC DYSPHONIA is a severe vocal disability in which a person speaks with excessively adducted vocal cords. The resulting weak phonation sounds tight, as if the patient were being strangled, and has also been described as laryngeal stutter. It is often accompanied by face and neck grimaces. In the past spastic dysphonia has been regarded as psychoneurotic in origin and has been treated with speech therapy and psychotherapy with disappointing results.

Because of laboratory and clinical observation that recurrent nerve paralysis retracts the involved vocal cord from the midline, it was proposed that deliberate section of the recurrent nerve would improve the vocal quality of patients with spastic dysphonia. In 72 patients the recurrent nerve has been sectioned after lidocaine (Xylocaine®)-induced temporary paralysis showed significant improvement in vocal quality. With nerve section in addition to postoperative speech therapy, approximately half of the patients have close to a normal but soft phonatory voice. In the rest there were varying degrees of improvement, but all, so far, have been pleased with the improvement in ease and quality of phonation and in reduction or elimination of face and neck grimaces. Two men have a breathy component in their phonatory voices, and one woman has variable pitch. In three patients spasticity has redeveloped 4 to 7 months postoperatively. In one of these the situation has been corrected by superior laryngeal nerve section.

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Daytime Sleepiness Caused by Nighttime Airway Obstruction

EXCESSIVE DAYTIME SLEEPINESS, especially in overweight men, can be caused by an intermittent airway obstruction during sleep. This sleep apnea syndrome has parallels with the better known but much less common pickwickian syndrome, and also can occur in children. The most important feature of this syndrome is that all of the patients we have encountered so far, and most of their physicians too, are completely unaware that

they have periodic obstructive episodes during their sleep. They notice only an increasing daytime lethargy, mental dullness, and a tendency to fall asleep in any routine or boring situation—while driving, during meetings, watching television and the like. In fact, the most common precipitating event leading to a referral to a sleep clinic is an automobile accident or several near misses because of sleepiness.

Snoring, usually loud and usually for several years, precedes other symptoms. Later on, pulmonary and systemic hypertension can develop. Children suffer in school performance, become enuretic, and have an increase in nightmares. In about a third of children and an occasional adult, the obstructive problem is related to very large tonsils. The most common cause, however, is an unexplained collapse of the hypopharyngeal muscles which occlude the airway. This obstruction is cyclic, lasting ten seconds to three minutes, and can recur as many as 800 times per night. Relief of the obstruction occurs with return of muscle tonus as the patient's level of arousal increases. However, because they rarely wake completely, they are never personally aware of the obstruction.

The final diagnosis can be made only by sleep polygraph recordings since this disorder must be distinguished from diaphragmatic apnea and narcolepsy. Tonsillectomy or tracheotomy, when symptoms warrant, are functionally curative.

In our experience, many physicians and most lay persons who encounter this syndrome only on a casual basis consider a tracheotomy a somewhat drastic treatment for daytime sleepiness. However, the patients themselves feel otherwise once freed of their obstructions. Not one patient has requested the tube be removed, including three physician patients.

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EDITORIALS

The Laetrile Nightmare

ELSEWHERE IN THIS ISSUE Lewis reviews the scientific data regarding the effectiveness of Laetrile (amygdalin) for the treatment of patients with cancer, and expresses some informed opinions about the desirability of its use. Although many studies have been done, there is no objective evidence that the substance is of any value in the treatment of cancer. Nor is there evidence that it is very harmful—unless given in large doses or in combination with certain other substances, when the poison, cyanide, can be released in the body. If this is true, and it is, then how is it that Laetrile is being so effectively promoted, and what if any are the implications of this popular phenomenon?

First of all there must be a motive other than the cure of cancer for the promotion and sale of this evidently worthless substance. In our still somewhat free enterprise system, profit would seem the most likely motive. In this system the aim is to find a need, fill it, and make a profit, or, if one is still more enterprising, create a need, fill it, and make a profit. There is presumably some real or imagined gain for those who contribute the dollars that create the profits. If not, they are victims, being unfairly or dishonestly exploited. In the case of Laetrile there is at least circumstantial evidence of profiteering at the expense of persons who are afflicted with a dread, often incurable disease, and who are sick, frightened and often desperate. There is little if any evidence of any real value received for the dollars spent, although in some cases there is perhaps some imaginary benefit.

At this writing public and legislative acceptance of the use of Laetrile in the treatment of cancer seems to be gaining ground. This is happening in spite of the fact that the Food and Drug Administration (FDA) and the responsible elements in the medical profession are all standing firm in the scientific position that Laetrile is useless in the treatment of cancer, and in the humanitarian position that its use serves only to give false hope to those afflicted with this disease, and to exploit the financial resources of often desperate persons. Yet the ground swell of public approval and acceptance continues to grow, in apparent conflict not only with scientific fact, but with highly touted social principles, and even laws, for the protection of the public from misrepresentation and exploitation. Clearly something other than consistent logic and rational behavior is at work.

Humans are so constituted that emotion can block out reason, if the emotion reaches a certain critical intensity. This is true not only for individual persons; because emotions are contagious, they and their accompanying irrationalities can spread quickly through groups and indeed whole populations. Skilled promoters, whether in business, advertising or politics, can manipulate this phenomenon. One can sense that something like this may be occurring with the promotion of Laetrile as a cancer cure. The contagion is spreading in the population at large—"if it doesn't do any harm they should have the right to try it"—and the hysteria (because it really is that) has begun to sweep legislators along with it, even though legislation to approve the use of Laetrile in the treatment of cancer is clearly and logically in conflict with the well-recognized article of faith that it is a responsibility of the legal system to protect the public from exploitation in what has become a highly complex technologic society.

The situation is irrational. For some of us it seems like a nightmare. But it is real. On the one hand society is leaning over backwards to protect consumers from exploitation and on the other it appears to be espousing once again the unfettered principle of "caveat emptor," and this in a

situation where a buyer is in a singularly poor position to exercise sound judgment about the value of what is being bought. It is a dangerous precedent to cast aside a body of human experience, garnered over decades, which has determined that in a complex technologic society the consumer should be somehow protected from unbridled exploitation in matters beyond his or her technologic ken. Irrationality is for real, manipulation of mass psychology is for real. These are the disturbing truths that surface when one awakens from this Laetrile nightmare.

—MSMW

Familial Mediterranean Fever—A Progress Report

THE SPECIALTY CONFERENCE from the University of California, Los Angeles, on familial Mediterranean fever (FMF) in this issue deserves special comment for several reasons. First, it evidences renewed clinical interest and rekindled research effort in a *rare* disease that promises to shed *no* light on cancer, arteriosclerosis, diabetes, or any other bête noire scheduled for caging via a categorical center grant. Second, the individual contributions serve to contrast sharply a redefined knowledge of the clinical manifestations of FMF (and their generally excellent response to an age-old nostrum) with our astonishing ignorance of the pathogenesis of the disease. Finally, there is the implicit suggestion that the "colchicine connection" may point talented sleuths in the proper investigative direction toward enlightenment concerning the underlying mechanism of FMF attacks.

Regarding the clinical features, there is a growing awareness that the Israeli version of FMF is not the only one. As noted by the UCLA group, amyloidosis is extremely rare in their cohort of Armenian patients, and this is also true of Jewish patients seen in the United States.[1] Many of them are Ashkenazi, rather than Sephardic Jews—a fact that has uncertain relevance to their freedom from amyloid deposition. Arthritis and skin manifestations are considerably less common here than in Israel.[1-3] The absence of a positive family history is probably more frequent among our sporadic cases, as compared with their endemic ones. Are we talking about the same disease? Decidedly yes—on the basis of its most important hallmarks: brief (1 to 3 days) and unpredictable attacks of abdominal pain and fever; rapid lysis to completely normal interval health, and the lack of an identifiable cause despite exhaustive diagnostic evaluation. Although it is premature to consider colchicine suppression a hallmark of the disease, its value to so many patients in the Mediterranean basin and in North America does support a unitarian concept of what is being called FMF in both regions.

The widespread use of colchicine treatment has sparked a newer set of observations. Most patients receiving suppressive therapy of one to three pills per day describe incipient attacks that are completely aborted by a single additional dose. Approximately 15 percent of patients with FMF show minimal or no response to colchicine. (The reason for this is as cloudy as why most patients *do* respond.) In particular, remission is less apt to be achieved in children, even at adult dosage. An early fear that chronic colchicine therapy might produce genetic damage appeared to be assuaged by a brief report from the Tel Hashomer group, which described normal offspring in seven "at risk" pregnancies that were followed through delivery.[4] Alas, they have since observed a child with Down's syndrome born to a mother who inadvisedly continued colchicine while pregnant.[5] Whether the current admonition to discontinue the drug three months before planned conception will be sufficiently protective remains uncertain. For this reason, the program of prodrome-initiated colchicine treatment described by Wright and coworkers[6] is an appropriate substitute for chronic prophylaxis in potential child-bearing patients whose attacks can be substantially aborted in this manner. The intimation that colchicine might reverse or prevent amyloidosis in FMF victims is based on very preliminary observations.[4] If borne out, this would be mind boggling indeed, especially in view of the purported *lack* of relationship between amyloidosis and the frequency or severity of FMF attacks.[3] Although it has been shown that colchicine pre-treatment can block casein-induced amyloidosis in mice,[7,8] the dosage required to achieve this is approximately a third of the lethal dose in these animals.

Finally, how might colchicine provide a clue to our understanding of the pathogenesis of FMF?

If there is any analogy to the gout story, our attention must surely be directed to the polymorphonuclear leukocyte as a crucial intermediary in the evocation and perpetuation of the inflammatory attack. Polymorphs have not only been identified as the dominant cell in FMF effusions, but a tantalizing photograph has even shown inclusion bodies (phagocytosed *what?*) within them.[3] The message for the investigator would seem clear: the material to be examined is probably not intravascular, but intraperitoneal, on occasion intrapleural, and rarely (in this country) intra-articular. But this is far easier said than done. It is an unusual FMF patient who is willing to discontinue taking colchicine, and a still rarer one willing to have peritoneal lavage done at the inception of his attack. (And how about the human experimentation committee?) But think of the potential yield to a hypothetical multidisciplinary group of investigators! There would be cells to examine by phase and electron microscopy for unusual ingestants, and supernatant to search for that elusive metabolite (the protagonist?) as well as the more fashionable mediators of inflammation such as products of complement activation, immune complexes and prostaglandins. Doubtless a lead would be gained, providing it was resolved to discount the inevitable viral particle or two that would peek out from an electron micrograph. By incubating harvested polymorphs, one might also learn whether the demonstration that they are unstable in certain unphysiological conditions is translatable to the *in vivo,* inflammatory milieu. A fanciful project? Perhaps. But to the extent that our understanding of the mechanism of gouty arthritis has emerged from a close look at what is occurring in joint fluid, so might one wish for some application of Sutton's law to the investigation of FMF.

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An Extended Role for Physician Extenders

THERE IS NOTHING really new about the concept of physician extenders. Well-trained professionals and assistants of many kinds have long been extending the reach of physicians in their offices, in the care of their patients in hospitals, and in many other settings. Practicing physicians simply could not serve their patients or the public as well as they do without this kind of assistance. This has been a natural development. Perhaps it is now high time to give more consideration to a further role for physician extenders—a role that would enable physicians, or groups or clusters of physicians, to surmount geographic, cultural, language and even economic barriers to making mainstream medical and health care available to those segments of the citizenry who do not yet have adequate access to it. This could be a further extension of the natural role of physician extenders.

Both the governmental (public) and the nongovernmental (private) sectors of our country have addressed these difficult problems over the years. So far the problems have not been very well resolved. In some ways they may even have been compounded. Private insurance for medical care solved some but not all the problems. Government funding of health care for the aged and the poor (Medicare and Medicaid) solved some but not all the problems—and unexpectedly created some new ones. For example, and really not all that surprising, the more dollars that were infused into the nation's health care system, the more the costs rose. The escalating costs are now becoming really frightening, and their control is about to take precedence over the basic purpose, which is to ensure that adequate (we used to say the best) care is available to persons who need it.

Among the populations which are yet to be reached adequately are those who are "remote" from the existing health care system because of what have been called "barriers," as though these were purposely erected to prevent access. Of course there was no such purpose. Rather the

barriers are geographic, cultural, language, educational and still sometimes economic, now more often because of limited availability of costly resources and less often because of inability to pay. In any case what about this remoteness and these barriers? The remoteness can certainly be geographic and pertain to sparsely populated areas which simply cannot support fully developed health care resources in every hamlet. But remoteness can also apply to an urban ghetto which may even physically surround a major medical center bulging with the most highly developed and costly resources for medical and health care. Here the remoteness or the barriers are not geographic, but they may be just as real—cultural, language, educational and still economic.

What is often overlooked is that physicians have a subculture of their own. They have their own language, education, and social, economic and human service goals, and they are willling to work hard for all of these. This subculture is actually worldwide, and has never been studied or discussed very much. But it is real. And this subculture does not interact easily with cultures or subcultures with different languages, education and value systems. These can be real barriers and they are not easily overcome by any of the parties concerned.

It is suggested that there is a further natural development of the physician extender concept. This would be to extend the role of physician extenders to surmount distance barriers where these exist and cultural barriers where these exist, and in this way link physicians (who these days must practice in a professional environment with adequate resources to do their task well) with patients in remote situations of whatever kind. The use of modern communications and transportation technology, together with appropriate clinical algorithms, such as those suggested by Charles and co-workers elsewhere in this issue, should make such an approach feasible. A group or cluster of physicians with a critical mass of resources and physician extenders, could serve a *remote* area of sufficient size to have an economic base large enough to support whatever services are needed to provide adequate access to today's mainstream of medical and health care. The alternative—independent practice by so-called second level practitioners who are in the wings and striving to gain acceptance—would seem to be a poor substitute for physician responsibility for patient care even in remote and underserved areas. Physician extenders, whether nurse practitioners (mostly women) or physician's assistants (mostly men), and modern communications and transportation technology, should be developed to provide truly mainstream medical and health care—under direct physician supervision—for those Americans who do not now have ready access to it. Nothing less should suffice—or be acceptable.

—MSMW

CASE REPORTS

Refer to: Burbige EJ, Bedine MS, Handelsman JC: Adenocarcinoma of the small intestine in Crohn disease involving the small bowel. West J Med 127:43-45, Jul 1977

Adenocarcinoma of the Small Intestine in Crohn Disease Involving the Small Bowel

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CHRONIC INFLAMMATORY DISEASE predisposes the development of carcinoma in the colon in persons with ulcerative colitis[1,2] and perhaps also in those with Crohn disease of the colon.[3] The relationship between carcinoma of the small intestine and Crohn disease, however, is not clear. It has been suggested that the finding of adenocarcinoma in the small bowel in association with Crohn disease may be of statistical significance.[4]

We have recently found adenocarcinoma of the small intestine in a patient with long-standing Crohn disease. We have reviewed the experience with small bowel adenocarcinoma and Crohn disease at The Johns Hopkins Hospital and in the literature in order to help establish the frequency of this occurrence.

Report of a Case

A 43-year-old white man had a 20-year history of cramping and diarrhea. Admission to hospital was required in 1957 at which time no operative procedure was done. In 1960 a mass was drained in the right lower quadrant without resection. In March 1961 ileal resection and an ileotransverse colostomy were carried out. Postoperatively, a fistula developed. An attempt at repair in 1963 was unsuccessful and a long enterocutaneous fistula developed. This was eventually repaired successfully. The patient was readmitted to The Johns Hopkins Hospital in July 1973 for evaluation of abdominal cramping and bloating occurring six to eight hours after meals. This was associated with fever to 102° F. Findings on a small bowel series included two areas of moderate narrowing at the anastomotic site with friable mucosa around the anastomosis. Biopsy studies of specimens obtained at colonoscopy showed acute and chronic inflammation with increased crypt mitoses. Specimens of both colonic and ileal mucosa were obtained.

Because of persistent obstructive symptoms, laparotomy was done. An abscess was drained from the mesentery of the terminal ileum with a fistula between the ileum and abscess noted. Approximately 25 cm of ileum was resected and an ileostomy was carried out. On pathologic examination of the removed portion of ileum, changes were noted that were consistent with Crohn disease. The ileum was notably thickened with an ulcerated wall containing sinus tracts, abscesses, chronic inflammation and scarring in all layers. A focus of adenocarcinoma (Figure 1) was found which seemed to arise in the base of an ulcer in the diseased part of ileum. The carcinoma was moderately well-differentiated and invaded the bowel wall, scar tissue, smooth muscle and perineural lymphatics. The carcinoma did not, however, reach the serosa. The ileal mucosa showed extensive pyloric metaplasia, but no epithelial changes resembling the "precancer" changes seen in ulcerative colitis.

The patient's subsequent course was complicated by several episodes of nephrolithiasis. The ileostomy was later taken down and continuity of the bowel reestablished. The patient has had an uncomplicated course since that time.

The Johns Hopkins Hospital Experience

From 1964 through 1973 there were 495 admissions for regional enteritis to The Johns Hop-

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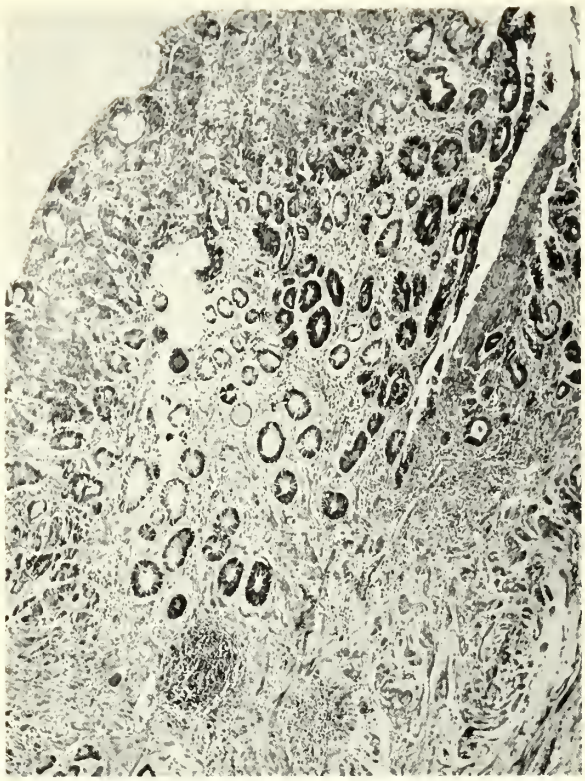

Figure 1.—Photomicrograph of resected ileum showing a focus of invasive adenocarcinoma (Hematoxylin and eosin, reduced from 50×).

kins Hospital. During that same period, there were 68 small bowel resections done in 64 patients with regional enteritis. There were two surgical specimens of duodenum, two of jejunum and 66 of ileum. The average age of this group of patients was 32.8 years. There were 34 females and 30 males. In one female there were three resections of the ileum and in two males there were two resections each of ileum. The most frequent reason for surgical intervention was the presence of fistula, second most common was obstruction and third was the presence of a mass. Carcinoma was found in only one resected specimen, that of the patient described in the above case report. During that same period, 11 primary adenocarcinomas of the small intestine were seen. There were two in the duodenum, five in the jejunum and four in the ileum. The average age at discovery was 53.7 years. There were four females and seven males.

Discussion

The first reported case of adenocarcinoma of the small bowel occurring in a patient with Crohn disease was described by Ginzburg and co-workers in 1956.[5] Since then, there have been 41 cases reported of adenocarcinoma of the small intestine in patients with Crohn disease.[5-17]

Carcinoma of the small bowel occurs with an incidence of 0.3 per 100,000 population per year.[18] The prevalence of Crohn disease is approximately 9 per 100,000.[19] The chances of the two diseases occurring simultaneously is put at no more than one in 1,000 million.[5] Fielding and associates[4] reviewed their experience with 295 patients having Crohn disease and found the incidence of malignancy higher than expected, but this was based on finding only one case. In their series of patients with Crohn disease several different malignant lesions were found, but only the higher incidence of cancer of the pancreas and small intestine were statistically significant (at the 5 percent level).

There are some striking differences between patients with primary small bowel malignancies and patients with Crohn disease in whom carcinoma of the small intestine developed. The average age of patients with small bowel tumors is 55 years and the duration of symptoms is 14 months. The mean survival has been described to be 32 months.[12] In 486 cases of primary small intestinal tumors, 215 occurred in the duodenum, 172 in the jejunum and 90 in the ileum.[20] In patients with Crohn disease in whom adenocarcinoma developed, the average age is 43.3 years, duration of symptoms is 14.5 months and average survival is only six months. In patients with Crohn disease, carcinoma developed more often in the ileum, a pattern more consistent with the distribution of Crohn disease rather than primary small bowel carcinoma. In 44 percent of reported cases, the carcinoma was found in a bypassed segment.[15]

Even a high index of suspicion may not increase the frequency of diagnosis. Radiologic investigation of surgically excluded segments of small intestine is quite difficult. Surgical operation may not be helpful, and the diagnosis is frequently made postoperatively by pathological examination, as was seen in the present case. One case was suspected preoperatively,[8] five cases were diagnosed at operation,[6,7,11-13] two cases were diagnosed postmortem and the remainder postoperatively. The most frequent reason for operation was intestinal obstruction in long-standing regional enteritis.

Although the number of cases reported in the literature suggests that this complication occurs more frequently than by chance alone, no indi-

cation of the true incidence can be obtained. Aside from the study by Fielding and co-workers,[4] reports have not given any indication of the population at risk. Since referral centers usually deal with more severe disease, the experience at one institution may not relate to all patients with regional enteritis. In order to obtain an idea of the incidence of this complication, the population at risk should be identified whenever a case is reported. The series reported here deals only with inpatients and since the follow-up of each patient is incomplete, only those operated on can be excluded as not having carcinoma. In order to obtain the incidence of adenocarcinoma in regional enteritis detailed studies of large groups, perhaps combining several institutions, with long periods of follow-up are necessary.

How regional enteritis predisposes to carcinoma is unknown. It may be that as in long-standing ulcerative colitis, long-standing inflammation leads to carcinoma. Weingarten and Weiss,[7] and Berman and Prior,[9] felt that long-standing inflammation preceding the malignant change served as evidence of an etiological relationship and suggested that the disease caused chronic irritation in the way that ulcerative colitis predisposes to carcinoma of the colon. The situation is not entirely analogous since no premalignant changes have been described in regional enteritis as they have been in some cases of ulcerative colitis. A possible explanation for the development of carcinoma is bile acid alteration resulting from bacterial flora changes and stasis. This may help explain the frequent occurrence in bypassed segments. A similar mechanism has recently been suggested as possibly playing a role in the development of colonic carcinoma.[21]

Malignant lesions other than small bowel tumors have been reported in association with regional enteritis. Carcinoma of the colon has occurred in patients with granulomatous colitis.[10,22,23] Three cases of reticulum cell sarcoma[4,24,25] in association with Crohn disease as well as one of carcinoid[26] have been reported. In addition, pancreatic carcinoma, carcinoma of the ampulla of Vater and esophageal carcinoma have been reported to occur in association with regional enteritis. At present, too few data are available to assess whether all these malignancies are related to the granulomatous process.

Patients with regional enteritis in whom adenocarcinoma of the small intestine develops are those with long-standing disease (more then ten years in most cases). They present with fistulae, intestinal obstruction, abdominal mass or with general deterioration. These factors should be considered by physicians caring for patients with chronic regional enteritis. When surgical operation is indicated bypass procedures should be avoided, if possible.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Informed Consent

TO THE EDITOR: I have read with interest the article entitled "Informed Consent—Is It Bad Medicine?" by Dr. Ronald Katz at page 426 of the May 1977 issue of the journal, and the editorial on the same subject at page 391.

I concur with most of Dr. Katz' article. Certainly human memory is fallible and patient retention of information given is erratic.

Most certainly, continuous research should be undertaken and the results published regarding the practical impact of patient care information, including psychological consequences and other result patterns that are relevant to medical care that follows the giving of information.

A patient should not be subjected to two or more independent lectures relating to a single episode of care that he is about to experience. I refer, of course, to the surgeon and the anesthesiologist separately and independently overwhelming the patient with what may happen to him.

On the other hand, I am constrained to comment on one bit of folklore that appears twice in the article. Dr. Katz states: "Having a signed consent form does not protect a physician." Again he states: "I further propose that we not force patients to sign meaningless pieces of paper to satisfy legal and bureaucratic requirements."

To begin with, a signed piece of paper is *not* what informed consent is all about, and no matter what is written on a signed piece of paper, it, in and of itself, cannot satisfy "legal requirements."

The doctrine of informed consent visibly entered California when the Supreme Court of the State decided *Cobbs vs. Grant* in October 1972. The essence of the Supreme Court's decision is contained in one sentence of the rather lengthy written opinion. I quote:

> Therefore, we hold, as an integral part of the physician's overall obligation to the patient there is a duty of reasonable disclosure of the available choices with respect to proposed therapy and the dangers inherently and potentially involved in each.

Please note (A) it is the physician's duty, (B) to make reasonable disclosure, (C) of available choices, and (D) dangers, if any, involved.

The court also stated that the duty of disclosure has various exceptions, such as emergencies, or where the patient is a child or incompetent, or affirmatively states a desire not to know, etc.

Unless the physician has made disclosure to the patient, no written or printed document, signed by the patient or not, can substitute for the duty of reasonable disclosure.

Institutions have traditionally felt a need to organize things in a standardized way so that the masses are all treated alike. Hence, the preoccupation with printed forms that everyone entering an institution willy-nilly must sign. No matter how beautifully phrased, or how "legally" constructed, they aren't worth the paper they are written on if no one bothered to tell the patient that which the Supreme Court has said the patient has a right to know.

In fact, uniform printed forms for patients' signatures are a snare and a delusion because they tend to lull physicians into a sense of security.

By far, the best evidence of an informed consent is a note made in the patient's medical record at the time of discussion between physician and patient that available choices, benefits and risks have been communicated to the patient, together with a very brief summary of the patient's response.

One final comment—it is quite possible that, as stated in the editorial, informed consent may prove to be another situation "in which the assumptions of the legal system run counter to the realities of human nature and human biology." If so, the courts will modify their present standard, but this will only occur if objective, believable research validly demonstrates to a reasonable mind that such is the case.

HOWARD HASSARD, Esq.
Hassard, Bonnington, Rogers and Huber
San Francisco

Grip Test for Pseudoacetylcholine

To the Editor: Lee and Nagel in their article, "Abnormal Sensitivity to Succinylcholine—A Possible Obstacle to Nerve Repair," which appeared in the April issue, state, "no screening tests [for pseudoacetycholine] have gained popularity, because they are costly, time-consuming, rarely rewarded and not readily available." I found this interesting because I developed a simple test many years ago.

The procedure for this "grip test" for pseudoacetylcholine is as follows: The patient's index and middle fingers are squeezed tightly by the doctor and the patient is told that this is a test that will not hurt. After three or four squeezes the patient is told to squeeze the doctor's index and ring finger of one hand tightly three or four times. The doctor then becomes aware of the tightness of the patient's grip. He next administers, intravenously, 2 mg of succinylcholine using a tuberculin syringe. He reassures the patient that there will be a mild dizziness or buzzing sensation in the face. At 20 seconds after administration of succinylcholine the patient is asked to squeeze the doctor's index and middle fingers once tightly to assess the degree of grip loss. This is repeated every ten seconds until the grip returns to normal at approximately 50 seconds postinjection. This test is carried out quickly, costs little and gives maximum results in one minute.

In the rare patient with a high titre of pseudoacetylcholine, the weakness of the grip may last from five to six minutes. Such a patient may require a few whiffs of oxygen.

In many thousands of electroshock treatments I have found only four patients who have required lower doses of succinylcholine due to a higher titre of pseudoacetylcholine. I have not required the use of any of the more esoteric tests available.

MORRIS I. VILKIN, MD
Inglewood, California

Controversy Over Nursing

To the Editor: The letter "Controversy Over Nursing" by E. R. W. Fox in the April 1977 issue was called to my attention early this month.

It's delightful to see an opinion that's less hysterical, more objective and certainly more optimistic than any I've seen or heard recently.

Medicine and nursing have always been the backbone of the health care team. Both professions have grown immensely in knowledge and responsibility. But we still need to work *together* for the benefit of the health care recipient.

I only hope there are enough clear thinking people like Dr. Fox in both professions to bring us through the storm with results that will benefit nursing, medicine and the patient.

PATRICIA JORY, RN
President, Idaho Nurses' Association
Boise

* * *

To the Editor: I want to take this opportunity to congratulate Dr. E. R. W. Fox on his insightful letter to the editor in the April issue. In my opinion he succinctly summarized some complex events of the past year and some glaring communication problems between our respective professions.

I appreciate the recognition of the potential contribution of well prepared clinicians in nursing. There are many fine nurses in Idaho who strive to develop collegial relations with physicians within a client-centered "marriage."

EILEEN H. ZUNGOLO, EdD
Chairperson
Department of Nursing
Idaho State University
Pocatello

Avocados—A Parable

Once upon a time the son of an eccentric inventor discovered a formula of his mother's, involving an emulsion of the avocado. Not being sure what to do with it, he cautiously approached several interested parties, including the Sons of the American Revolution and the Committee for Freedom of Choice in Automobile Accessories. A decision was made to sell the emulsion as an additive to the gas tank, with claims of longer mileage and smoother-running engines. This attracted the attention of the Automobile Manufacturers Association, the Federal Trade Commission, the Interstate Commerce Commission, gasoline companies, and automobile mechanics. The massive opposition by the automobile-transportation-industrial complex forced the promoters to change the label of their product to a preservative, to be sprayed on the dashboard. Word-of-

mouth spread that the emulsion could prevent or moderate accidents or injuries, and in hearings before the National Transportation Safety Committee, hundreds of persons gave personal witness to being saved from injury or death by applying Avocado Emulsion to the dashboards of their cars, boats, airplanes, motorcycles and even skateboards. Many went so far as to remove seat belts entirely from their vehicles, and most said wearing the belts was unnecessary, even if drunk while driving (nothing was heard from any person who had been killed while driving *and* using the product). Testimonials filled the newspapers and magazines, although no actual conclusive data could be discovered. Attorneys general and district attorneys followed the seesaw battle, uncertain whether or whom to prosecute. Civil liberties, free enterprise, the scientific method, democracy, right-to-drive and the status of foreign bank accounts all were at stake.

Finally, the Supreme Court of the United States ruled that Avocado Emulsion was a *food* and *must* be sold in *all* supermarkets. As soon as the product appeared on all the shelves, the public quickly lost interest, and the issue died out.

Thus was the Republic preserved.

RICHARD E. TIRRELL, MD
San Pablo, California

Medi-Cal Benefits Out of California

To the Editor: The California Medicaid program (Medi-Cal) would like to offer the following basic claims information to physicians and medical facilities located outside of California as an aid in obtaining reimbursement for furnishing medical services to California residents eligible for medical assistance.

Benefits are provided for *necessary* out-of-state medical care within the limits of the program only: when an emergency arises out of an accident or illness; when the health of the individual would be endangered if care and services were postponed until the patient returned to California; when it is customary practice in border communities for California residents to use medical resources in adjacent areas outside the state, and when an out-of-state treatment plan has been received, reviewed and authorized by the State Department of Health *before* the services are provided.

Types of service available are hospital inpatient and outpatient care; physician's services; drugs and medical supplies; X-ray and laboratory studies; ambulance; and prosthetic/orthotic appliances and assistive devices.

All nonemergency out-of-state services require prior authorization. Emergency services are defined as treatments or procedures provided a beneficiary for the alleviation of severe pain or for immediate diagnosis and treatment of unforeseen medical conditions which if not immediately diagnosed and treated would lead to disability or death. Nonemergency services are defined as services that *do not* require immediate attention as defined under emergency services. These services must have authorization from the California Medi-Cal Consultant before billing the fiscal intermediary. Requests for authorization should be directed to: State Department of Health, Office Administrator, Medi-Cal Field Office, 100 Mission, Room 900, San Francisco, CA 94111.

Claims without eligibility documentation for the *exact* month of service being billed *cannot* be paid. Patient's eligibility can be documented with a copy of the Proof of Eligibility (POE) label or copy of the patient's identification card.

Fiscal intermediary provider number application forms are required in order to facilitate timely computer claims processing and reimbursement. Applications may be obtained from the listed intermediaries.

Fiscal intermediaries who provide Medi-Cal billing instructions are:

Medi-Cal Communications, Out-of-State Unit, Blue Cross of Southern California, 4777 Sunset Boulevard, Los Angeles, CA 90027, (213) 666-7280.

MIO Provider Inquiry, Blue Shield of California, P. O. Box 7924, Rincon Annex, San Francisco, CA 94120, (415) 445-5701.

Medi-Cal Out-of-State Unit, Blue Cross of Northern California, 1950 Franklin Street, Oakland, CA 94659, (415) 645-3226.

In communicating the foregoing information, we hope to relieve difficulties that frequently have been encountered by non-California providers when services were administered to Medi-Cal beneficiaries.

JAY A. GOULD, *Chief*
Fiscal Intermediary Section
State of California
Department of Health
Sacramento

Trauma Rounds

Chief Discussant
JAMES WILSON, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Wilson J: Wound ballistics (Trauma Rounds). West J Med 127:49-54, Jul 1977

Wound Ballistics

JAMES MALONE, MD:* The case for presentation today is that of a 17-year-old boy who presented to San Francisco General Hospital with a .357 magnum gunshot wound completely through the right upper quadrant of the abdomen at the level of the right costal margin in the midclavicular line. The hole of entrance was dime-sized (1.5 cm) and the hole of exit was quarter-sized (2.5 cm).

The patient was in profound shock upon admission and, after appropriate resuscitation was carried out, laparotomy was done promptly. On operation, massive disruption of the liver with a 10 cm defect in the center of the liver substance between the two lobes was noted. The circulation to the liver was isolated by clamping the portal triad. Debridement of the liver, repair of several large defects in the suprarenal vena cava and right nephrectomy were then carried out and drainage was accomplished through the bed of the 12th rib. The patient's course has been relatively benign and he is about to be discharged now, ten days postinjury.

Sponsored by the American College of Surgeons Northern California Trauma Committee. Supported in part by NIH Grant GM18470.

*Chief Trauma Resident, San Francisco General Hospital.

Reprint requests to: Donald D. Trunkey, MD, Department of Surgery, 3A, San Francisco General Hospital, San Francisco, CA 94110.

F. WILLIAM BLAISDELL, MD:† *I would like to introduce one of our senior surgery residents, Dr. James Wilson. Dr. Wilson received training in small arms while in the Navy and became particularly knowledgeable in the use of the M16 rifle and the .45 automatic pistol. He became interested in the science of ballistics during this period.*

JAMES WILSON, MD:‡ I suggested to Dr. Malone that he present this case because a number of the members of our trauma team, after examining the entrance and exit wounds, were surprised at the extent of the internal damage. In this instance, the liver received the brunt of the injury and literally was exploded by the missile.

I believe that all of us who deal with gunshot wounds must have some understanding of ballistics if we are to manage patients with such injuries properly and if we are to avoid all lethal secondary complications which may result from bullet wounds. Unfortunately, the science of ballistics is a very complex subject that receives little attention in peacetime and usually has rela-

†Chief, Surgical Service, San Francisco General Hospital; Professor of Surgery, University of California, San Francisco.

‡Senior Resident, Surgical Service, San Francisco General Hospital.

tively little application in the management of civilian peacetime injuries. The reason for this is that most gunshot injuries we see in civilian situations are wounds from relatively low velocity missiles secondary to the use of handguns.

The mechanism of injury due to low velocity bullets was described as early as 1862 by MacLeod, who based his comments largely on observations made in the field during the Crimean War. In 1848 during Paris street fighting, Hugier observed the bursting effect of high velocity missiles on soft tissue and postulated that this was due to water particle dispersion in the tissues. Kocher then tested this hypothesis experimentally in 1876. In 1894 Horsely confirmed Kocher's studies, theorizing that the extent of damage correlated directly with the amount of fluid in the tissue.

The concept of cavitation was borrowed from hydrodynamics and was first applied to wound ballistics in 1898. Cavitation is the formation of a vacuum as a result of a solid object moving rapidly through a gas or fluid. In 1910 Stevenson described the shearing effect on blood vessels present in high velocity wounds and in 1921 Wilson described the effects of the formation of a temporary cavity on blood vessels, noting that slit-like lesions occurred in areas of the artery distal to the bullet track. Wilson also noted similar lesions in cases of near misses. In 1953, during the Korean conflict, Jahnke and Seeley described microscopic lesions occurring in vessels adjacent to grossly injured segments. These observations helped to explain the high failure rate of primary arterial anastomoses carried out without debridement of adjacent ends.

Interest in wound ballistics has been rekindled with the advent of the revolutionary 5.56 mm (M16) rifle in the late 1950's and with the current use by many police departments (including that of San Francisco) of magnum revolvers. Some state police units and special groups such as S.W.A.T. (Special Weapons And Tactics) units are now also using hollow point bullets and M16 rifles.

The increasing use of these higher speed bullets together with their more destructive characteristics make it imperative that civilian as well as military surgeons understand the basic principles of ballistics. Indeed, military surgeons, by virtue of the nature of the Geneva Convention, will likely treat wounds caused by fully jacketed bullets, while civilian surgeons in a country where hunting is a favorite sport have the greatest likelihood of encountering the most devastating wounds of all—those inflicted by ultra-high-speed hollow point bullets.

Ballistics is the study of projectiles in motion and can be divided into three categories: internal, external and terminal ballistics.

Internal Ballistics

Internal ballistics is the study of the passage of the bullet within the gun barrel. The hammer of the gun strikes the fulminate-of-mercury primer which ignites the slower burning powder in the casing, causing the bullet to separate from the casing. The force (or pressure) created by the expanding gas is what propels the bullet. In handguns pressures of up to 40,000 pounds per square inch (PSI) can be reached and in rifles pressures of up to 70,000 PSI may be generated. In view of these facts, it is not difficult to envision how the use of too large a powder charge or of an incorrectly-matched ammunition and handgun combination could cause a weapon to explode, causing serious injury. As a result it is most important that the magnum principles be understood.

A magnum charge simply means that more powder is present in the casing. For example, the only difference between a .38 caliber and a .357 magnum bullet is that the latter shell has more powder in it. As a result of the increased amount of powder, this type of bullet must be fired from a gun designed to withstand the higher pressures generated by it. Consequently, it is apparent that .38 caliber ammunition can be safely fired from a .357 magnum revolver, but not vice versa. Incidentally, for those unfamiliar with the term "caliber," it refers simply to the diameter of the bullet expressed in inches.

Most guns have longitudinal grooving, or rifling, in the barrel. This rifling imparts a spin to the bullet as it exits and this helps to stabilize it in flight. This spin can be greater than 200,000 revolutions per minute.

External Ballistics

As the bullet leaves the barrel, two very important measurable factors come into play: muzzle velocity (or the speed of exit of the bullet) and muzzle energy (determined by the mass and the velocity of the bullet). These measurements, together with the flight characteristics of the bullet, are dealt with in the science of external ballistics.

The efficiency a bullet has in overcoming air resistance in flight can be expressed numerically and is called the ballistics coefficient. It is related to the sectional density and nose shape of the bullet. Additional factors such as drag retardation and rotational energy also come into play, but these lie beyond the scope of this discussion.

In short, the killing power of a projectile is largely determined by the kinetic energy level upon impact. It follows that this killing power will be greater with bullets having higher ballistics coefficients.

One final aspect of external ballistics is important in our present discussion. This has to do with the actual physical flight of a bullet, since the aerodynamic forces acting upon a spin-stabilized bullet can contribute significantly to the wounding power of that bullet. Yaw, the deviation of the bullet's longitudinal axis from the actual line of flight, is a most important factor here because it directly influences the projectile's overturning moment in the target tissue; a bullet will tumble if its overturning moment due to yaw is sufficiently large. Other factors such as precession (or the lateral spinning around the center of mass) and nutation (the rotational movement in circles progressing in a rosette pattern) are also important. All of these influences together help make the wound inflicted by the M16 rifle (the standard military weapon) so devastating.

Terminal Ballistics

Terminal ballistics or wound ballistics is a science which deals with the amount of energy imparted to the tissues by a missile. This is determined primarily by calculation of the striking velocity and by the shape and weight of the bullet, although velocity is by far the most significant factor of these. Three theories have been formulated for quantitating wounding capacity: the *momentum theory,* which states that momentum is equal to the mass of the bullet times velocity; the *power theory,* which says that power is equal to mass times velocity raised to the third power, and the *kinetic energy theory,* which states that kinetic energy equals mass times velocity squared, all divided by two times gravity. The latter theory is now thought to provide the best estimate of wounding capacity and it follows from its application that modest increases in velocity will result in tremendous increases in the kinetic energy of the missile. Recognition of this fact led to the development of the new lightweight but powerful military rifles such as the M16, whose caliber (.223) is quite small.

Upon evaluating the impact kinetic energy of a missile, we see that both mass and velocity play important roles in determining the actual wounding capacity. Taking mass first, it is obvious that increases in mass will increase the impact energy. The .45 caliber automatic pistol, which has been standard issue of the United States armed services since 1911, was developed with precisely this principle in mind. At that time, the velocity factor of the equation was unalterable—powder and chamber steel had not yet advanced enough to enter the magnum era. Ballistics experts examined the ability of the then-standard .38 special revolver (used before the .45) to wound enemy personnel and found that even when solidly hit, an enemy might not be immobilized. Therefore, it was concluded that by increasing the mass of the bullet to the 240-grain weight of the .45 missile, the desired wounding effect could be achieved. A present-day comparison of bullets shows the importance of mass differences between the .357 magnum and the .44 magnum. Both travel at approximately the same velocity—about 1,500 ft per second. But the .357 bullet weighs 158 grains while the .44 bullet weighs 240 grains. This mass difference accounts for the diverse muzzle energy values for these two missiles—845 ft-lb and 1,150 ft-lb respectively.

The amount of energy imparted to the tissue may be estimated as the kinetic energy upon impact minus the kinetic energy upon exit. It is here that actual bullet design becomes important and the great difference between battlefield and civilian wounds is readily seen. Ideally, a bullet should dissipate all of its energy to the tissue with no residual exit energy. The severity of a wound, then, is directly related to the amount of kinetic energy absorbed by the tissue from the bullet. The level of energy absorption at a tissue depth of 15 cm in humans is used as the index of wounding capacity, as this is the depth at which most vital structures lie. Therefore, missiles which disintegrate upon impact or which have great penetrating ability such as those designed for elephant hunting are inappropriate for military use, as these types of bullets would pass right through the target object without releasing any significant amounts of energy.

Types of Bullets

Bullets are divided into three basic types: lead, semijacketed (hollow point or soft point) and fully-jacketed. The lead bullets utilize maximum mass while maintaining minimum air resistance. When equipped with a magnum charge of powder, they are the standard issue cartridge used by the San Francisco Police Department—the .357 magnum lead bullet. This type of bullet will impart most of its energy to whatever it strikes since it becomes deformed after impact and therefore the danger of innocent bystanders being injured by bullets passing through the target object is minimal. However, due to the low melting point of lead, these bullets cannot be propelled beyond a velocity of about 2,000 feet per second (FPS).

Therefore, for higher speed missiles, one must use jacketed bullets. These usually have a lead core with a copper-nickel jacket although steel is sometimes used when high penetration is desired, as when automobiles or armored vehicles are likely targets. Semijacketed bullets with lead noses or hollow points are designed to mushroom after initial penetration, thereby dissipating more energy to the tissues. With the use of an expanding bullet—that is, a hollow point—the advancing frontal area of the bullet after impact can achieve impact values ten times greater than those of a fully-jacketed bullet.

In some states, police use hollow points to achieve greater immobilizing ability. These are usually used in conjunction with a magnum load, since it has been shown by Dimaio and others that standard loads like that of the .38 special do not generate enough velocity (or kinetic energy) to enable the hollow point to wound any more effectively than the more conventionally designed bullets.

Fully-jacketed bullets are mandatory ammunition for military use as designated by the Geneva Convention. With the use of these bullets, the penetration (especially with high velocity weapons such as the American M14 and the Russian AK47) becomes much greater with less damage to the tissue, since less kinetic energy is absorbed. An exception to this is in the case of the M16 at higher velocities; so-called "lead splatter" will occur—that is, even though the missile is fully jacketed, its velocity is so great that it may disintegrate in its course through the body.

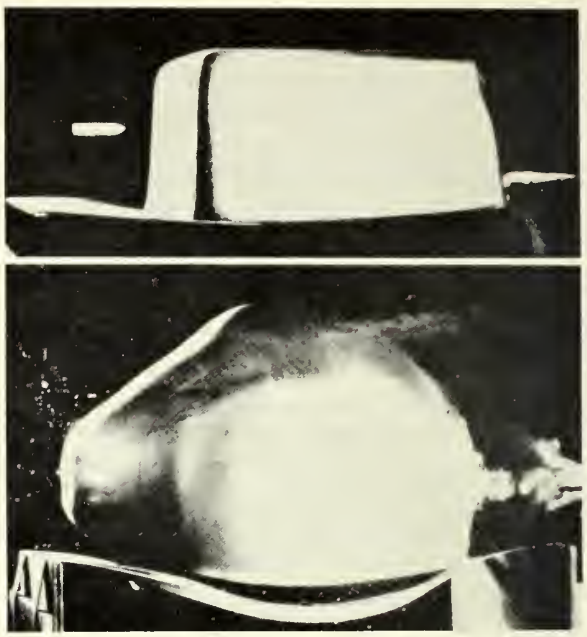

Figure 1.—High Velocity Injury. **Top,** Bullet is shown approaching a suspended gelatin block, **Bottom,** Bullet has emerged from the right of the gelatin block. The tremendous explosive or cavitation effect is exemplified by the simulated tissue. (Reproduced by permission of author and publisher from Amato JJ, Billy LJ, Lawson NS, Rich NM: Am J Surg 127:454, 1974)

Bullet Velocity

Now we come to the most important part of the kinetic energy equation—velocity. Bullet velocity is probably best classified as low (if less than 1,000 ft per second), medium (if in the 1,000 to 2,000 range) and high (if the velocity is greater than 2,000 ft per second). The muzzle velocity of a given weapon is determined by the weight of the bullet and the powder charge, while impact velocity will be determined, of course, by these factors together with the range or distance of the target from the weapon.

Low velocity wounds do little damage other than in the direct pathway of the bullet, for only a small temporary cavity is formed. In fact, as was noted by MacLeod in 1862, blood vessels can actually be pushed aside by low velocity missiles.

Medium and high velocity wounds may be grouped together for purposes of this discussion. Medium velocity bullets such as the .357 magnum and the .44 magnum create larger temporary cavities and a greater blast effect than do the low velocity bullets like the .22 or .38—but not nearly to the extent as that seen with high velocity weapons such as the M16 or the .30-06.

A high velocity bullet releases energy upon

impact, which creates a temporary cavity (Figure 1). This phenomenon is known as tail splash and the energy released is transmitted to tissue particles with rapid acceleration, both in a forward direction and laterally. Consequently, these particles then push forward and expand the cavity laterally to up to 30 times the size of the entering bullet and pressures of up to 3,000 pounds per square inch can be reached during the few milliseconds of cavity formation. The cavity begins to form 1 to 2 msec after impact and the missile undergoes several pulsations of decreasing amplitude before it comes to rest, resulting in the permanent track—the only damage apparent to the surgeon at the time of debridement of the wound. As mentioned earlier, the type of tissue and the pathway of the bullet are also important factors. Indeed, the pattern of injury is largely determined by the density, elasticity and cohesiveness of the tissues penetrated.

The high elasticity of lung tissue helps to protect it from the damage accompanying creation of the temporary cavity; the cavity in lung tissue is much smaller than that seen in muscle, liver or bone tissues. But this is not to say that no damage is done. The shock wave alone from higher velocity bullets such as the M16 causes massive destruction of cellular integrity.

Muscle and liver are two types of tissue with very similar densities and the energy absorbed per cubic centimeter of tissue for both muscle and liver tissue is essentially the same. Both exhibit tail splashing when penetrated, but only a small area of destruction surrounding the temporary cavity will ultimately be seen with muscle wounding even though initial tissue displacement might be extensive. Since liver tissue has less cohesiveness than muscle tissue, the formation of the entire temporary cavity will result in obvious external damage, manifest by gross disruption, as occurred in the case just presented. Therefore, the permanent cavity will approximate the size of the temporary cavity. The spleen has this same characteristic.

Some debate has ensued over the existence of a temporary cavity in instances of high velocity bone injuries. However, some cavitation is probably the case. As is obvious, when bone is struck the boney fragments themselves become missiles, producing even more damage. As you might imagine, even large bones may be fractured though not directly struck by a high velocity bullet.

DR. BLAISDELL: *Dr. Wilson, would you mind spending a moment describing the particular principles of ballistics involved in vascular injuries?*

DR. WILSON: Vascular injuries are a special category. Damage to areas of vessels remote from the actual track often occurs. In one experiment a steel sphere fired at 3,000 feet per second into a femoral artery suspended in gelatin produced a shearing injury for several inches along either side of the direct path of injury. In similar studies, the artery suspended in gelatin was severely damaged by cavitation even when an M16 bullet passed several inches away. The lesions produced secondary to cavity formation add to the total destruction of tissue in the direct path of the bullet. These vascular injuries consist of loss of endothelium, microthrombus formation, breaks in the internal elastic membrane and outward herniation of the media.

DR. BLAISDELL: *I have found it helpful to envision vascular injuries as the artery being forcibly stretched to several times its normal length in the area of injury. The adventitia or outer coat of the artery is the toughest and most durable part, and the intima (inner coat) the least. This "stretch injury" results in a transection of the intima and a variable portion of the media, and the shearing effect causes the intima to roll up like a windowshade in both directions from the center of the injury. This leaves denuded vessel walls with variable degrees of intimal obstruction on both sides of the injury.*

DR. MALONE: Dr. Wilson, as you know, we do not carry out much debridement of missile tracks associated with most handgun injuries that we treat. Would you comment on the principles of debridement? How radical should this be?

DR. WILSON: As I indicated, low velocity missile injuries such as those associated with .22 or .38 caliber handguns produce an injury much like a simple stab wound. The police magnum pistols, however, produce a much more extensive soft tissue injury, and debridement of the missile track back to viable bleeding tissue should be done. In high velocity rifle injuries, survival following truncal injuries is rare. Injured extremities require extensive debridement and often amputation.

DR. BLAISDELL: *I agree entirely with Dr. Wilson's comments. Frequently, however, the nature of*

the injury is such that the surgeon may have difficulty carrying out adequate debridement. This includes problems over areas such as vital organs, mesentery, retroperitoneum and pelvis. At the initial operation, all grossly nonviable tissue should be removed. Then reoperation should be carried out within 12 to 24 hours to reassess the tissue damage and to complete the debridement of any tissue which has become nonviable. This should be repeated as often as necessary until all nonviable tissue is removed. In some instances, Marlex® mesh may be necessary to close abdominal wall defects so created.

Dr. Wilson, do you have any closing comments?

DR. WILSON: It is clear that high velocity wounds can cause extensive damage beyond that which is immediately apparent in an emergency room or operating theatre. Just as it is important to know the mechanisms of a burn injury, it similarly is extremely helpful to know, if possible, the caliber and type of bullet used to inflict the injury.

In most criminal trauma cases, the exact nature of the weapon used to inflict the injury will not be known. However, an attempt has been made here to give you the knowledge to make an educated guess as to the potential of the wound you will treat.

Two Opinions on the Diagnosis of Chronic Hepatitis

When should you suspect chronicity in a patient treated for acute hepatitis?

DR. BOYER: "I think if a patient has evidence of abnormality of liver function for more than three months, one should find out what kind of hepatic abnormality you are dealing with. Now, of course, you want to exclude the more common causes, such as alcohol abuse and biliary tract disease, but in many of these patients, that is the point at which we would advise the patient to come in for a liver biopsy to settle the issue if we cannot exclude chronic hepatitis on clinical grounds. So I use a definition of about three months, which is really based on what we know about the normal time course for acute viral hepatitis to resolve. And most cases, of course, will be resolved within that time limit."

DR. REYNOLDS: "Well, I wouldn't disagree with trying to find out at somewhere around the three-month level, all circumstances permitting, but having seen a number of patients in whom the condition dragged on as long as nine months and then seemed to resolve totally, I would like to extend that period of time considerably before I would be very confident of chronic disease—extend it months, and maybe a year."

DR. BOYER: "I didn't mean to imply that these patients all have chronic disease. I think many of them will turn out not to have chronic disease."

DR. REYNOLDS: "There's nothing wrong with trying to find out at three months, I agree. And particularly if the antigen remains positive for more than about 10 to 12 weeks. This is very suggestive that things are not going to heal up completely."

—JAMES L. BOYER, MD, *Chicago*
TELFER B. REYNOLDS, MD, *Los Angeles*
Extracted from Audio-Digest Internal Medicine, Volume 22, Number 12, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

Refer to: Lewis JP: Laetrile (Informed Opinion). West J Med 127:55-62, Jul 1977

Informed
OPINION

Laetrile

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LAETRILE (amygdalin or vitamin B_{17}), unlike krebiozen, its sister drug of the 1950's, continues to have its advocates. During the early part of 1977, some 20 state legislatures considered bills designed to legalize Laetrile (personal communication from C. Dahle, American Cancer Society, California Division, Inc., San Francisco). In California, Senate Bill 245 was introduced to legalize the administration of Laetrile and, in addition, to make it legal to combine this drug with "any vitamin, mineral, enzyme, or any food for special dietary use deemed adjunctive or necessary to Laetrile therapy when prescribed by a physician and surgeon."[1] Also, this bill would legalize the manufacturing of the drug. Pressure groups behind this movement have been reported elsewhere[2] and data proving it is not a vitamin[3] but a quack cancer drug[4] have appeared earlier in this journal. Lacking firm evidence that Laetrile is beneficial in the treatment of persons with cancer, one can only assume that it is the profit motive that keeps this nostrum in the public eye. Indeed the profits accruing to smugglers and sellers of the drug are reported to be substantial.[5]

As a part of the propaganda program mustering support for Laetrile, it has been suggested that: *(1) no progress has been made in cancer treatment for the past two decades, therefore why not try Laetrile,*[6] *(2) Laetrile has never been truly tested in this country because the American Cancer Society and other elements of the "establishment" wish to suppress cancer cures for fear of going out of business,*[7] *(3) Laetrile is completely harmless and nontoxic and in a free society patients should be permitted to treat themselves with any harmless medication they believe effective*[8] *and (4) it is legal in many countries and patients outside the United States benefit significantly from treatment with it.*[7]

The net effect of these claims has been to rally modest support from a broad base of the American public, including physicians. The latter group, in general, have supported the legalization of Laetrile if for no other reason than to remove the profit motive[9] and to provide some hope for terminally ill cancer patients who are frustrated by the inability to receive a drug that they believe may be effective.

In this paper, I will review the scientific data refuting these widely held concepts and then will cover a few issues that portray the negative impact Laetrile's legalization will have on the quality of medicine and health care in our country.

Support for Laetrile Lacks Credibility

Contrary to the statement that no progress has been made in cancer treatment for the past two decades, Recent Trends in Survival of Cancer Patients[10] *shows that substantial progress has been made in all 17 tumor types indexed.* The percent increase in five-year survival rates ranges from 0 for one disease only (histiocytic lymphoma in males) to 700 percent for acute lymphocytic leukemia in females. The average increase in five-year survival for all patients was 75 percent.

This statement on Laetrile was adopted unanimously by the Cancer Advisory Council of the State of California on May 11, 1977. The material used in this article was offered in testimony against SB 245 before the California State Health and Welfare Committee on March 30, 1977 and before the California Board of Medical Quality Assurance on April 15, 1977. In these hearings Dr. Lewis represented the California Medical Association.

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Progress reflected by these nationwide studies may be directly attributable to improvements in cancer detection, improvements in surgical techniques, and implementation of higher energy radiation therapy. In some cases such as childhood acute leukemia, these data also reflect progress in chemotherapy. Nevertheless, the major advances in the past decade in chemotherapy are yet to be adequately recorded by this survey. For instance, at present histiocytic lymphoma is being successfully treated with a 48 percent complete remission rate and most of these patients do not relapse.[11] In addition, these figures do not reflect totally the impact on survival and cure of the multidisciplinary approach to the cancer patient. Most surely with an updating of the end-result studies we can anticipate even higher percentages of improvement for each cancer cell type. On the other hand, no data have ever been published showing that Laetrile is useful in any type of cancer. Rather the data suggest that Laetrile is a nontreatment for this highly lethal group of diseases.

Contrary to the statement that Laetrile has never been adequately tested,[7] *the record shows it has been investigated extensively.*[12-25] The conclusion of each study has been that Laetrile is totally worthless. The development and identification of effective chemotherapeutic agents in cancer rely upon studies showing activity of the proposed chemotherapeutic agent in animal tumor systems, as well as in Phase I and II clinical studies. In such systems Laetrile has been found to be inactive. The following summarizes animal and clinical studies on Laetrile:

- In 1953 the first article appeared in the literature using Laetrile in animal trials.[12] Four separate studies were reported utilizing C1300 neuroblastoma tumor in A-mice, acute lymphatic leukemia in DBA line 2 mice, Crocker sarcoma 180 tumors in mice and ear tumors in mice. None of these tumors responded to Laetrile.
- Data from the National Cancer Institute's Testing Program on Laetrile summarized in 1975 included studies done in 1957, 1960, 1969, 1973 and 1975.[13] In these investigations, Laetrile was either tested alone or in combination with its cyanide cleaving enzyme, beta-glucosidase. The following tumor types were investigated for response to Laetrile treatment: carcinoma 775, sarcoma 180, leukemia L1210, Walker 256 carcinoma, lymphoid leukemia P388, B16 melanoma, Lewis lung carcinoma and Ridgway osteogenic sarcoma. "In each of the tests . . . , the compound failed to produce a reproducible antitumor effect."[13]
- As part of the McNaughton Foundation's submission for an investigational new drug application in 1970, other animal studies were reported.[14] These had been done by the Scind Research and Development Company, Inc. of San Francisco, California. These studies were carried out on the L1210 mouse leukemia, the S180 tumor, CA755 adenocarcinoma and Walker 256 tumor systems. Waldemar R. Gustavson, Executive Vice President, Scind Research and Development, in a letter to Mr. McNaughton dated October 18, 1968, stated "We are in a position to draw the following conclusions: (1) Laetrile when administered without beta-glucosidase has *little or no effect* upon the transplanted rodent tumor systems tested, (2) beta-glucosidase when administered without Laetrile has *no effect* upon the transplanted tumor system tested, (3) Laetrile when administered in conjunction with beta-glucosidase has a *highly significant effect* upon the tumor system tested" (emphasis theirs). "We are pleased to state that the above is in accordance with predictions by the McNaughton Foundation." Again, therefore, Laetrile by itself was shown to be ineffective. Why it appeared active when combined with beta-glucosidase is not known. When these studies were repeated by others, this beneficial effect was not confirmed.[13,15,16]
- By 1975 the Arthur D. Little Company had studied Laetrile in L1210, P388, B16 and the Walker 256 tumor systems.[15] Again, Laetrile failed to show a positive effect. The combination of Laetrile plus beta-glucosidase resulted in potentiation of amygdalin's toxicity. In that same year, the Southern Research Institute reported on their studies with the Lewis lung tumor, the Ridgway osteogenic sarcoma and the P388 tumor. They reached the same conclusions—Laetrile was without antitumor activity.[16]
- In 1976 the Washington University School of Medicine investigated the effect of Laetrile alone on the B16 tumor and the BW5147 AKR leukemia and confirmed again that Laetrile was inactive in these systems.[17]
- Recently studies from Sloan-Kettering Institute using transplantable and spontaneous murine tumors have been reported by C. Chester Stock.[18] These studies again show no response. "We have tested amygdalin at high doses, 1,000 mg/k/day, in over a dozen transplantable tumor

systems and one induced tumor system without seeing any action against the tumors. The chemotherapeutic agents effective in clinical cancer have had or would have had their activities detected in one or more of those systems." This report corrects the controversial report "leaked" to the press in 1973 suggesting Sugiura's studies at Sloan-Kettering showed Laetrile to be beneficial.[19] Dr. Stock, in commenting on follow-up studies to Sugiura's preliminary investigations, goes on to state, "Subsequent experiments, in some of which Dr. Sugiura participated, some conducted in conjunction with Dr. Daniel Martin of the Catholic Medical Center of Brooklyn and Queens and some which were independent by other investigators in our Institute, showed that the initial results were not consistently observable. In some experiments there were more metastatic mice in the treated than in the control mice. In the latest experiment in which Dr. Sugiura read the lungs of the mice without knowing what treatment they had received, there was essentially no difference found between the treated and control groups. In summary, not even the spontaneous mammary tumor experiments offer me encouragement to recommend amygdalin for clinical trial."[18]

- Limited studies have also been conducted with three dogs and one cat with naturally occurring tumors (personal communication with W. D. Hardy, Memorial Sloan-Kettering Cancer Institute, May 1977). No antitumor effect was observed when Laetrile was administered at a dose of 100 mg per kg of body weight per day given intravenously six days per week for five weeks. The cat with mammary adenocarcinoma and two dogs with mammary adenocarcinomas were treated for five and six weeks respectively. One dog with renal carcinoma was treated for two weeks. It was found that 1 mg per kg of body weight per day of Laetrile given to healthy dogs intraperitoneally was tolerated well, while an oral dose of 100 mg per kg was lethal within three days.

In summary, Laetrile has failed as an active chemotherapeutic agent in the usual acceptable animal tumor screens that classically have been utilized to identify potentially active anticancer drugs. From this, one would predict that Laetrile would be inactive in man. Clinical studies in humans published to date tend to confirm this impression:

- In January of 1953 the Cancer Commission in California obtained clinical data on 44 patients with cancer who had been treated with Laetrile.[12] Supposedly these data were selected to show the beneficial effect of this drug. At the time of the report, 19 had died of their disease. Seven were lost to follow-up and had cancer at the time they left the study. Seventeen patients were still alive, six of whom may have had static disease, eight had progressive disease, and three were terminal. One patient had no evidence of cancer. She was a woman with preinvasive epidermoid carcinoma of the uterus. This was initially diagnosed on biopsy, but on rebiopsy was not verified. None of these 44 patients had objective evidence of control of cancer under treatment with Laetrile alone. These patients in whom stabilization of disease was seen were receiving other forms of chemotherapy or had received radiation. In nine of the 19 patients who had died by the time of the report, autopsy studies were done and tissues examined by five different pathologists. They all agreed that there was no evidence of any chemotherapeutic effect on the tumor at the time of autopsy.
- In 1957, Dr. Navarro, an Assistant Professor of Biochemistry from Manila, published results of Laetrile in 14 patients with cancer.[20] These cases were published without controls and no evidence of prolongation of life was offered. In that same year, Dr. Navarro reported on 83 patients he had treated with Laetrile.[21] The length of survival of his patients ranged from 7 to 24 months. No evidence was provided that this was an extension of life for these patients. In both of his articles, Dr. Navarro stressed that "Laetrile is hydrolyzed by the hydrochloric acid in the stomach; hence, it should never be given by mouth."
- In 1962 an attending surgeon at Jersey City Medical Center, Dr. John Morrone, published a brief report of ten patients treated in the United States with Laetrile. His conclusions were that there was a possible regression of tumor in some of these patients. His data were incomplete as no data were provided on the effects of Laetrile on overall survival.[22]
- In 1970 the Contreras Clinic assembled 702 cases treated with Laetrile.[23] Of these, 62 patients died within the first three weeks of treatment. No explanation is given for the cause of death in these patients, although it is impled that death was secondary to cancer. Dr. Contreras thought that several types of cancer might be treatable with Laetrile with response rates between 30 and 35 percent. These so-called responsive tumors included cancer of the prostate, lung, breast and

uterus, and lymphoma. After one year of treatment, however, only 23 of the 702 patients (approximately 3 percent) appeared to have benefited from Laetrile treatments. Of some concern in his report was the fact that 3.6 percent of the patients died of undetermined causes. Dr. Contreras himself noted that one patient after taking 6 grams of Laetrile orally experienced acute intoxication with vomiting, dizziness, slight cyanosis and headache. In addition, other patients had an allergy to this substance. From his data, one can only conclude that any responses patients might have experienced with Laetrile were indeed exceedingly brief.

- In 1970 Hans Nieper of Germany wrote on 35 cases of patients with cancer treated with Laetrile.[24] In contrast to Dr. Navarro,[20,21] Dr. Nieper felt that orally given Laetrille was considerably more effective than the intravenously administered preparation. Reading through his case reports, there may be five or six of his 35 patients that had some objective improvement. Since these patients were receiving other therapies in addition to Laetrile, it is difficult, if not impossible, to know which agent should be credited with any objective response. One patient with a brain tumor was made decidely worse with Laetrile; in addition, some patients experienced nausea following ingestion of the drug and some noted increase in nerve pain.

- In 1970, the McNaughton Foundation submitted an investigational new drug (IND) application for the clinical study of Laetrile. The animal studies reported in this application have been alluded to earlier.[14] In addition, clinical data were submitted. These data were considered insufficient to warrant the issuing of an IND license. One year later an ad hoc committee of oncology consultants for the review and evaluation of amygdalin appointed by the Food and Drug Administration reviewed this application and stated "Clinical material on the present IND 6734 does not fulfill minimal requirements for such decisions as to human efficacy. This committee would welcome the opportunity to review such material, including case reports, which will substantiate claims in an effort to assist the proper evaluation of amygdalin MF."[25] To date no such cases have been submitted to the Food and Drug Administration.

These human data parallel the animal tumor screen data that failed to show a beneficial response to Laetrile. This confirms the validity of the animal screen approach to the selection of potentially active chemotherapeutic agents.

In hopes of collecting additional data from clinics that presently prescribe Laetrile, one of my associates wrote to Dr. Contreras of Mexico, Dr. Hans Nieper of Germany and Dr. Navarro of the Philippines. Responses from all three Laetrile proponents have been received. Each letter reads essentially the same; they have no new data.

Contrary to being completely harmless and nontoxic, Laetrile is a poison. Amygdalin (Laetrile) contains cyanide, a respiratory enzyme poison. In humans, 200 mg of cyanide is toxic. Three grams of Laetrile contains 180 mg of cyanide. Cyanide is released from amygdalin in the presence of beta-glucosidase. If one ingests foods containing beta-glucosidase with Laetrile tablets, cyanide is cleaved and evidence of cyanide poisoning occurs. Quoting from Harrison's textbook *Principles of Internal Medicine,* "The cyanide ion is an exceedingly potent and rapid acting poison . . . . Parts of many plants also contain substances such as amygdalin which release cyanide on digestion. Among these are the seeds of certain stone fruits (choke cherry, pin cherry, wild black cherry, peach, apricot, bitter almond), cassava roots, etc. . . . As little as 300 mg of potassium cyanide may cause death."[26] Examples of toxicity and fatalities follow:

- In 1942 in the *American Journal of Medical Science,* four cases of cyanide poisoning following ingestion of seeds were reported in Indians in the western United States.[27]

- In 1960 four cases of cyanide poisoning were reported from France following the ingestion of amygdalin.[28]

- In 1961, again in the French literature, a case of a 4-year-old French girl was reported who became comatose after consuming ground-up peach seeds.[29]

- In 1964 the experience at Children's Hospital in Ankara, Turkey was reported, again pointing to the hazardous effect of ingestion of kernels of bitter almond. They reported nine cases of cyanide intoxication which required admission of the patients to hospital; two of these patients died. The poisoning was identified as being secondary to the ingestion of apricot seeds. The incidence of cyanide poisoning secondary to ingestion of apricot seeds was essentially the same as that of poisoning secondary to salicylates.[30]

- In 1965 a fatal case of cyanide poisoning was reported following ingestion of bitter almonds.[31]

• In 1969 a similar but nonfatal case of cyanide poisoning was reported following the ingestion of bitter almonds.[32]

• In 1972 an article was published in the foreign literature of another fatal case of cyanide poisoning following the ingestion of amygdalin.[33]

• In September of 1972, in *California Morbidity,* a weekly report from the Bureau of Communicable Disease Control, a case of cyanide poisoning was reported following ingestion of apricot kernels purchased from a health food store.[34] The story is indeed most informative. "A man and his wife purchased a two-pound bag of apricot kernels at a local health food store. They soaked some 30 kernels with dried apricots in distilled water overnight and the following day pureed the ingredients in a blender. The resulting concoction was bitter and took some effort to swallow. About an hour after drinking the mixture, the wife complained of abdominal discomfort, tachycardia, and feeling strange. She drank some water and vomited. Within minutes of his wife's onset, the husband became symptomatic also and complained of headache, lightheadedness, tachycardia, a generally strange sensation, and impaired vision . . . 'as if looking through frosted glass.' He felt impending doom. They were rushed to the emergency room of a nearby hospital. Vomiting was successfully induced, and after several hours of observation they were released. For the next three days the husband complained of insomnia and tinnitus. The wife had diarrhea which abated in one day. Both recovered fully."

• In November of 1975 a case of cyanide poisoning associated with forceful vomiting, headache, flushing, heavy perspiration, dizziness and faintness was reported in a man who had ingested 48 apricot kernels.[35]

• In December of that same year, another case of cyanide poisoning following ingestion of apricot kernels was reported in California. In this case a woman ate a "handful" of apricot kernels purchased at a "nutrition center" in Santa Clara County and within 30 minutes headache, rapid heart rate, a light-headedness, flushing and generalized weakness developed. Cyanide was identified in her serum.[36]

• In reading the literature from the Laetrile proponents, one cannot help but be impressed with the variety of toxic effects this drug produces, including fall in blood pressure,[21,22] itching,[20,22] free hemoglobin in the urine, hemorrhage into the gastrointestinal tract and the tumor,[20] fever,[20,21] and occasionally an increase in neuritis.[24] Also reported are vomiting, dizziness, slight cyanosis and headache.[23] When Laetrile is injected with beta-glucosidase, other side effects are seen, such as coughing, a sense of suffocation and pain in the lumbar region.[21] I have recently spoken with one of my patients who has been to the Contreras Clinic and she tells me that she too experienced nausea when taking oral Laetrile. Another patient has told me that several persons at the Contreras Clinic had serious reactions to Laetrile injections, including diarrhea, vomiting and high fevers.

• As regards chronic toxicity, we really have no data. There are statements that neuritis is made worse by administration of Laetrile;[24] this suggests that it may be chronically toxic to the nervous system. This has been adequately shown in Africa following cassava root ingestion. Cassava root contains an amygdalin-like substance which leads to severe nervous system dysfunction.[37] Long-term ingestion of this cyanogenic compound has also been postulated to be goitrogenic.[38]

• Another area of toxicity that is of considerable concern is the effects on fetuses. A teratogenic effect of Laetrile was suggested by the McNaughton Foundation in their 1970 IND application.[14] In these investigations pregnant rats were fed 5 or 25 mg per kg of body weight per day of Laetrile orally. Offspring of these rats were then studied for deforming effects of Laetrile. In rats given no Laetrile, one fetus was found to have a kidney abnormality. In rats receiving 5 mg per kg of Laetrile orally, one fetus was found to have a kidney defect, and two fetuses with abnormal kidneys were found in rats fed 25 mg per kg orally. In addition, one fetus from the group receiving 5 mg per kg orally had hydrocephalus. These findings would suggest that this drug may have an adverse effect on a developing fetus, and although it might not be as bad as thalidomide, additional studies are needed before this drug could be released for human consumption by pregnant patients.

• Some have suggested that, if legalized, Laetrile should be used only on hopelessly ill patients with cancer. These patients, however, present special problems which have not been adequately investigated. For instance, the acute toxicity of Laetrile in tumor-bearing animals is much greater than is the acute toxicity of Laetrile in non-tumor-

bearing animals.[14] This suggests that the more tumor that is present, the more toxic the Laetrile becomes. Consequently, in patients with far advanced cancer extreme toxicity might occur when Laetrile is given. In addition, these patients invariably have liver and renal damage either secondary to the tumor or to some metabolic dysfunction associated with their basic disease process. Laetrile is detoxified by rhodenase which is found in high levels in the liver. Is this same high level found in a cancerous liver? We have no data on this. The water-soluble benzaldehyde and cyanide moieties are excreted by the kidney. What is the effect of kidney failure on Laetrile's toxicity? Again, the data are not available.

In summary, Laetrile has a myriad of toxic effects in man and in some cases ingestion of amygdalin is fatal. It is hard to reconcile these facts with the cry of the Laetrile advocates that Laetrile should be legalized because this is a free country and freedom of choice demands that nontoxic drugs, even though not efficacious, be available to all who wish them.

If use of Laetrile is legalized for terminally ill patients, it will be used soon by patients with potentially curable disease as well. These patients, because of the adverse publicity that proponents of Laetrile have given to standard effective therapy (cutting, burning and poisoning), will be diverted from beneficial therapies to ineffective Laetrile. Ineffective treatment for early disease preempts ethical physicans' opportunities to cure cancer. According to a conversation* with Robert Bradford, President, Committee for Freedom of Choice in Cancer Therapy, Inc., fully 50 percent of patients going to practitioners who prescribe Laetrile have early disease. When asked if he meant by this that patients with Stage I Hodgkin disease, isolated breast tumors or small neoplastic colon polyps were receiving Laetrile, the answer was "Yes, isn't that wonderful!" It is also true that patients who are seen by Laetrile doctors do not undergo standard staging procedures nor do they receive accepted forms of treatment plus Laetrile. Patients seen in the medical oncology clinics at the Sacramento Medical Center confirm this. Those of our patients who have received Laetrile illegally in Mexico or California have not been properly worked up and evaluated, nor have they received other forms of therapy for cancer.

If states choose to make Laetrile a legal drug for terminally ill patients, it is only natural that patients will assume that if it is good for the terminally ill, it will be good for the minimally ill, and then finally it should be released for prophylaxis against cancer. Therefore, initial legalization, even though it may be highly restrictive, will soon lead to indiscriminate use of this drug since the proponents of Laetrile have been quite vocal in recent years proclaiming this as a prophylactic drug against cancer. Furthermore, legalization of Laetrile for the terminally ill suggests that critically ill patients are not entitled to our usual consumer protection laws; these laws prevent the use of worthless drugs in the treatment of disease.

In small doses, orally given Laetrile may not be harmful, but when ingested with uncooked foods such as fresh apples, sweet almonds or bean sprouts—which contain the beta-glucosidase enzyme—cyanide may be released, with the patient suffering the effects of cyanide poisoning (personal communication with Eric E. Conn, PhD, Professor of Biochemistry, University of California, Davis, April 1977).

Contrary to Laetrile proponents, this drug is not legal and freely prescribed in many countries. In 1975 and 1976 the following countries were contacted by Dr. Sherwood Lawrence, Executive Secretary, Cancer Advisory Council, Department of Health, State of California: Israel, Australia, Greece, Belgium, United Kingdom and India. Each of these countries had been reported at one time or another to have legalized Laetrile.[6] Responses from the Secretaries of Health or the equivalent from each of these countries stated that Laetrile was not legal and that no applications had been made to legalize it. In view of the proximity of Mexico to the United States and of the commonly held belief that it is widely utilized in that country, it is pertinent to quote from a letter dated August 21, 1975, from the Secretary of Health and Assistance of Mexico to Dr. Lawrence. The translation states that the direct selling of amygdalin to the general public is prohibited; it is available only to investigators, hospitals or clinics with the intention of continuing investigations; it was only permitted to be advertised as an "analgesic in some forms of lung cancer." They further state that Laetrile's analgesic effect is not comparable to that of narcotics. Recently the Mexican government has moved to terminate the

*At a meeting on October 25, 1976, in the offices of Governor Brown of California, attended by myself, Sherwood Lawrence, MD (Executive Secretary, Cancer Advisory Council, Department of Health), and two members of the Committee for Freedom of Choice in Cancer Therapy, Inc., including Mr. Bradford.

production of Laetrile because it has not been shown to be of value as a cancer remedy and it is this claim that accounts for the sale and exportation of amygdalin in Mexico (personal communication from the United States Embassy in Mexico to Secretary of State, Washington, D.C., April 1977).

The Negative Impact of Laetrile's Legalization

Bills such as those being promulgated in California formalize a new type of physician, one who practices "holistic medicine." Such a person is freed from ethical standards and made immune to prosecution as long as he practices within his confined field. Senate Bill 245, amended April 14, 1977, in effect legalizes the introduction of ineffective treatments for human disease.[1] This runs counter to the practice of ethical medicine and also strikes at the very heart of our solid research programs and broad-based medical education system, which attempts to bring effective therapies to the forefront.

It seems incongruous at a time when our gross national product devotes 8.3 percent to health care delivery that we would be considering the interjection of worthless treatments into clinical medicine. This will only raise costs and, of course, with the delay in treatment associated with Laetrile's administration, patients will be appearing with more advanced disease for standard therapy. The latter type of patient is certainly more costly to manage than is a patient with early disease.

The federal government, through the Kefauver-Harris Drug Amendments of 1962, prevents the interstate shipment of drugs that are merely safe but ineffective. State legislatures at this moment are attempting to circumvent this consumer protection law by providing for the manufacture, sale, prescription and use of Laetrile within state confines. Consequently the protection afforded us by the federal government through the Kefauver-Harris Drug Amendments becomes null and void. This suggests that many of the nostrums of the past decades may once again be manufactured and distributed on druggist shelves.

The State of California, through its Board of Medical Quality Assurance, attempts to provide continued surveillance of the qualty of medicine that is practiced within the state. Organized medicine has become active in Professional Standards Review Organizations (PSRO) in an attempt to upgrade the quality of medicine. Bills legalizing Laetrile and other worthless remedies essentially emasculate Boards of Medical Quality Assurance and make meaningless PSRO activities. The passage of Laetrile legalization bills makes it impossible to protect the public from the quasi-ethical and the unethical practitioner.

If a completely useless drug can be promulgated for the treatment of a highly lethal yet potentially curable disease, it is likely that additional useless drugs will find their way into the market place through state legislative actions for treatment of incurable chronic diseases, such as heart disease, diabetes, arthritis and the like. This is definitely a step back into the sordid past of medical history where quacks could be found providing useless devices, services and remedies for a variety of ailments.

Not to be overlooked is the fact that Laetrile as a worthless remedy is a ripoff. From conversations with my patients, I am led to believe that an average patient in California pays approximately $2,200 for six months of treatment with Laetrile. One of our patients has spent more than $4,000 for Laetrile treatment over the past 18 months. During this time, while away from standard forms of therapy, her initial Stage III-A nodular sclerosing Hodgkin disease with a greater than 61 percent five-year disease-free interval response rate has progressed to Stage IV-B with a less than 27 percent five-year disease-free response rate.[39] Therefore, for a $4,000 investment in her "nontoxic treatment," she has lost at least a 30 percent chance of being free of disease at five years. Since the tumor now involves her spinal cord and she is paraparetic, she may never walk even if we are successful in arresting her disease at this point.

Summary

In this report I have examined the facts about Laetrile. I find not a shred of evidence that this drug will play even a minor role in oncology in the future. The drug is toxic, at times highly so; it is teratogenic; it may be goitrogenic; it may cause deaths; and all animal and human cancer studies reported to date have failed to show prolongation in survival or a substantial reduction in tumor size.

Legislation responsive to Laetrile's pressure groups has the real potential of diverting patients with treatable and curable cancer away from the skilled care of competent physicians toward less knowledgeable practitioners who believe more in the propaganda of pro-Laetrile fanatics than in the current data showing real progress in cancer

treatment. With the passage of bills legalizing a worthless remedy for a eurable disease, we see a preeedent being set that will lead to a reorientation of our entire health care services, a reorientation away from effieaeious therapies toward useless nostrums. Let us hope our medical and legal professions will see the issues clearly and be guided by facts, not fantasy.

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A Physician Extender Training Program Based on Clinical Algorithms

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The ability of physician extenders to provide patient care in a variety of settings has been reported widely. Less attention has been paid to training programs, especially those of short duration, for physician extenders. A three-month training program for physician extenders at a large teaching hospital was based on teaching the skills needed to run 39 clinical algorithms. The course content and the methods used to test the students during the three months may prove of value to those preparing similar programs.

INCREASED INTEREST in physician extenders (such as nurse practitioners, MEDEX, child health associates, physician's assistants) is reflected by the growth in the number of training programs and in the number of publications about the effectiveness of these health professionals. The educational or training programs may be divided into three general types. The first, and best known, is a formal university program patterned after the methods and techniques used to train physicians.[1,2] The second type is usually shorter than the formal university programs and is often intended for registered nurses.[3] Two distinguishing features of the third type (which often is not a formal university program) are its short length and its reliance on a set of clinical algorithms (also called protocols). Most of the program is directed at teaching physician extenders the skills required to operate the clinical algorithms.[4,5] A clinical algorithm may be defined as a set of unambiguous, step-by-step instructions for solving a clinical problem.[6]

The content and training methods of the formal university programs may be obtained from university brochures and catalogs. Some information is available about non-university-based training programs for nurses.[3] However, much less information is available about the curriculum and training methods used in programs based on clinical algorithms. This paper presents such information.

The differences among the three kinds of programs reflect differences in educational goals of program administrators. The primary goal of formal university programs and nurse practitioner programs is to prepare health professionals who have the ability to work in a relatively independent though not autonomous manner. Although specific skills are taught as part of the program, the graduates of these programs acquire a sufficient body of knowledge to permit them to function effectively when faced with novel situations as well as to handle a wide range of common problems. Such an education might be called "theory based." In con-

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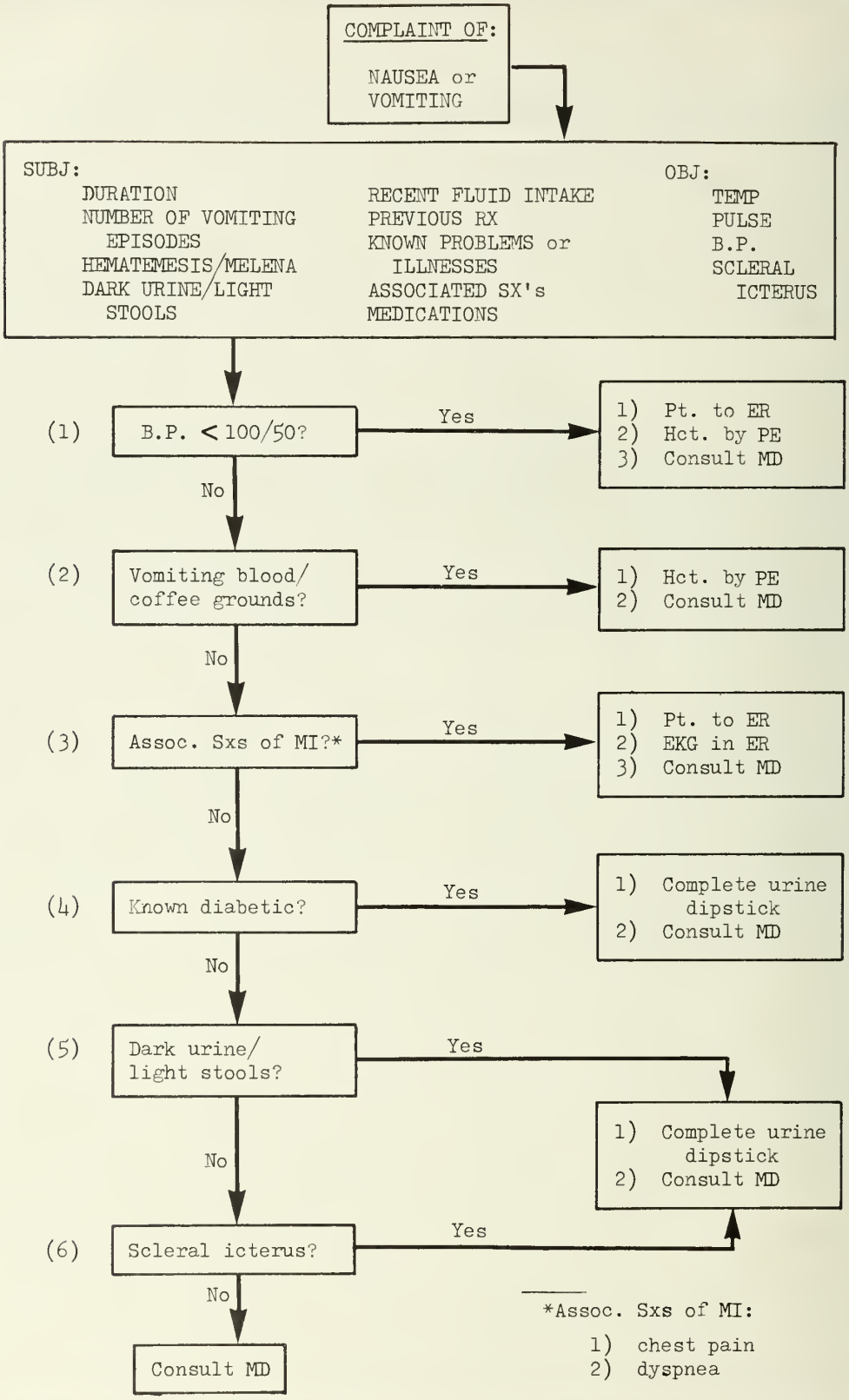
COMPLAINT OF:
NAUSEA or VOMITING
SUBJ:
DURATION
NUMBER OF VOMITING EPISODES
HEMATEMESIS/MELENA
DARK URINE/LIGHT STOOLS
RECENT FLUID INTAKE
PREVIOUS RX
KNOWN PROBLEMS or ILLNESSES
ASSOCIATED SX's
MEDICATIONS
OBJ:
TEMP
PULSE
B.P.
SCLERAL ICTERUS
(1)
B.P. < 100/50?
Yes
1) Pt. to ER
2) Hct. by PE
3) Consult MD
No
(2)
Vomiting blood/ coffee grounds?
Yes
1) Hct. by PE
2) Consult MD
No
(3)
Assoc. Sxs of MI?*
Yes
1) Pt. to ER
2) EKG in ER
3) Consult MD
No
(4)
Known diabetic?
Yes
1) Complete urine dipstick
2) Consult MD
No
(5)
Dark urine/ light stools?
Yes
1) Complete urine dipstick
2) Consult MD
No
(6)
Scleral icterus?
Yes
No
Consult MD
*Assoc. Sxs of MI:
1) chest pain
2) dyspnea

trast, the primary educational goal of short-term programs based on clinical algorithms is to prepare health technicians whose primary abilities are to carry out a set of tasks. Situations that fall outside the set of tasks are referred to physicians. Such an education is more limited than the other two and might be called "skill based."

Training Program: Methods and Curriculum

The 12-week training program for physician extenders at the San Francisco Veterans Administration Hospital was designed to prepare them to work under physician supervision in the drop-in clinic of the hospital. In this clinic the physician extenders collect information from patients, do certain procedures, record information and test results in a problem-oriented format, and present these data to physicians who make the decisions regarding patient care.

Persons with previous medical experience as military medical corpsmen, nursing aides, hospital orderlies, or licensed vocational or practical nurses were recruited for the training program. A key factor in selecting persons for the program was evidence of past success in some endeavor. Ability in verbal communication and desire for advancement were other important factors considered. To obtain this information, applicants were interviewed, personnel files reviewed where available, and past supervisors contacted. No age requirements were imposed and the students ranged in age from 22 to 47 years.

The curriculum of the 12-week program was based on 39 clinical algorithms.[7] These algorithms had been constructed to handle the most common presenting complaints of patients at the drop-in clinic of the San Francisco Veterans Administration Hospital. These 39 complaints accounted for 94.5 percent of all visits to the drop-in clinic. Table 1 shows the ten most frequent complaints.

TABLE 1.—*Ten Most Frequent Presenting Complaints at Drop-in Clinic*

Complaint	*Percent of Total Complaints*
Needs prescription refilled	16.9
Joint or extremity pain (atraumatic)	9.0
Abdominal pain	6.6
Chest pain	5.8
Skin (dermatologic) problem	5.7
Back or neck pain (atraumatic)	5.3
Eye problem	4.5
Nonpenetrating trauma (orthopedic)	4.2
Wants "check up"	3.4
Lump or swelling	3.0

An example of a clinical algorithm, together with its logic documentation, is given in Figure 1. As can be seen, this algorithm for the presenting complaint of nausea or vomiting defines the sequence of steps to be followed by a physician extender to collect the data a physician will need for subsequent handling of this problem. The clinical algorithms used in the drop-in clinic address only the task of providing data to the physician; they do not include the treatment portion of the patient's problems. However, more complicated algorithms have been used successfully and safely in a variety of situations to allow physician extenders to provide treatment for minor, self-limited illnesses or stable chronic diseases.[8]

Figure 1.—Clinical algorithm for complaint of nausea or vomiting. The following is the logic documentation for the algorithm.

Vomiting is defined as the regurgitation of the solid or liquid contents of the gastrointestinal tract. Nausea is defined as the sensation that vomiting might occur. The many causes of nausea or vomiting range from such serious conditions as bleeding peptic ulcer, acute bowel obstruction or diabetic ketoacidosis to such minor conditions as motion sickness or "flu syndrome." In addition, protracted or intractable vomiting itself can lead to serious dehydration and electrolyte disturbances. The physician is expected to evaluate the problem of protracted or intractable vomiting and its possible consequences. Significant abdominal pain will be evaluated using the abdominal pain algorithm because of the many possible causes of this symptom. The algorithm deals with the problem of nausea or vomiting as follows:

1. Blood pressure less than 100/50. A hematocrit is done by the physician extender while seeking immediate physician consultation because of the possibility of shock.

2. Vomiting blood or coffee ground material. A hematocrit is done by the physician extender and evaluated by the physician to determine the significance of the bleeding.

3. Associated symptoms of myocardial infarction (chest pain, dyspnea). An electrocardiogram is done in the drop-in clinic and will be evaluated by the physician. Since vomiting very often produces diaphoresis, this symptom alone in this algorithm will not be considered grounds for doing an electrocardiogram.

4. Nausea or vomiting in a known diabetic patient. Urinalysis and a urine acetone study is done by the physician extender and will be evaluated by the physician because of the possibility of ketoacidosis.

5. Dark urine or light stools. A urine specimen is checked for bile and will be evaluated by the physician for indication of liver disease.

6. Scleral icterus will be handled in the same way as possibility 5.

Because clinical algorithms identify the skills required by physician extenders to use the algorithms, a training program may be developed based on teaching these skills. For example, to use the clinical algorithm in Figure 1, physician extenders must have the ability (1) to obtain certain historical data from the patient, (2) to take the patient's vital signs (such as pulse, temperature and blood pressure), (3) to recognize scleral icterus, (4) to obtain a sample of blood for a hematocrit reading, (5) to do a hematocrit determination, (6) to obtain a standard 12-lead electrocardiogram and (7) to carry out a dipstick urinalysis. In addition, the physician extenders must understand the terminology used in the algorithm. The totality of skills required to operate all 39 algorithms defined the major portion of the training program reported on here.

Figure 2 is a graphic representation of the eight major components of the training program. As the figure shows, instruction based on the clinical algorithms began during the first week and continued throughout the entire 12 weeks. The other components related to the algorithms or to the environment in which the physician extenders would be working. Orientations to the hospital and to the drop-in clinic are examples of curriculum components related to the work environment.

A programmed text in medical terminology was used to broaden the students' understanding of the terminology used in the algorithms and to build their medical vocabularies so that they could communicate effectively with physicians and nurses.[9] A discussion of medical and professional ethics needed by all care givers was included in the first week of the program. Problems caused by the introduction of a new role or new type of care provider into a complex organization were also discussed during the first week and at periodic intervals during the remainder of the training program. Time was scheduled during each week of the program for discussing individual reactions to the program and any difficulties encountered.

Starting in the sixth week, the students were introduced to laboratory testing procedures (such as doing a hematocrit determination) and technical procedures (such as phlebotomy, obtaining an electrocardiogram) that the algorithms required. Periodic reinforcement from the 9th through the 12th week maintained proficiency in these procedures until full-time work in the drop-in clinic started. The students spent four weeks ob-

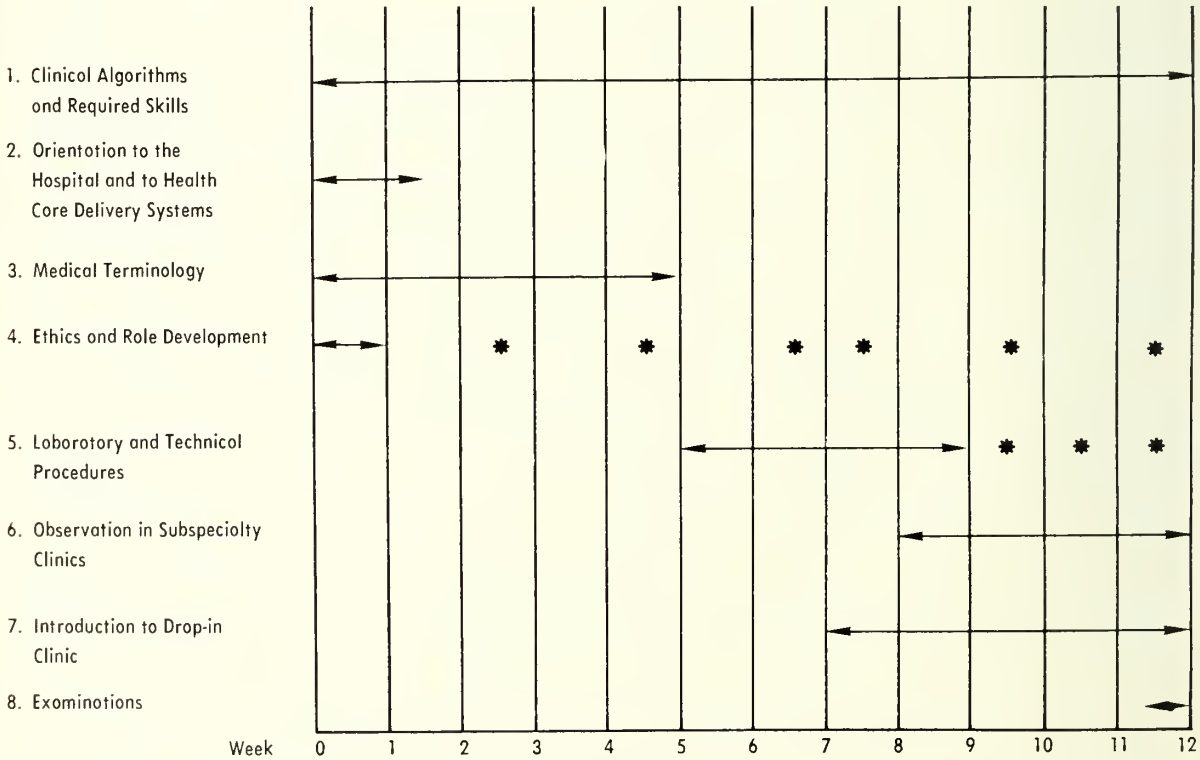

Figure 2.—Components of the twelve-week training program for physician extenders.

serving the operations of various subspecialty clinics (for example, an ear, nose and throat clinic) in order to gain familiarity with clinics to which they would be referring patients and in order to learn specific techniques (for example, irrigation of ear canal). During the seventh week the students began to work one day a week in the drop-in clinic. They were closely supervised by the full-time physician responsible for the training program. The clinic experience allowed the students to show their knowledge of the algorithms and required skills as well as introducing them to the personnel and procedures of the clinic in which they would work upon completion of the training program. Finally, time was set aside for examinations during the last week of the program.

Assessment of Student Progress

Much of the assessment of student progress was based on daily observations by the full-time physician in charge of the training program. When instruction was given by persons other than this physician (for instance, personnel in the eye clinic gave instruction in tonometry), these persons reported to the physician in charge of the program on how well the students did. Several other methods were also used to evaluate student progress. These included formal audits of the students' use of clinical algorithms in seeing patients, comparisons of findings on physical examinations done by students with those done by physicians, and scores on a final examination at the end of the program.

An important aspect of clinical algorithms is the ease of auditing the work of care providers who use the algorithms. Such use of clinical algorithms is well documented.[6] The audit was helpful in determining if the students understood the terminology used in the algorithms, adhered to the algorithms' logic, and collected the data and did the procedures required by the algorithms. The audit was done in the following manner. The students submitted a carbon copy of the written record of each patient encounter. From these records the auditor randomly selected ten records per student per week and manually checked the carbon copy of the record against the clinical algorithm. Data collection errors and decision logic errors were noted. The auditor, who was the physician in charge of the program, discussed the results of the weekly audits with the individual students. In this way, those areas in which students needed help were found quickly and arrangements were made to remedy weaknesses. By the end of the 12 weeks all the students were proficient in their use of clinical algorithms.

Another way of assessing student performance involved physical examinations. The procedure was to have a student and a physician not associated with the program carry out a physical examination on the same patient on the same day without either knowing of the other's findings. The scope of the physical examination was related to the skills required by the 39 algorithms. Forty physical examinations, each involving 37 examination points, were done. There were, therefore, 1,480 examination points on which to compare student performance with physician performance. Of the 1,480 points there were 1,370 agreements between student and physician (an average of 34.2 per examination), 63 disagreements (an average of 1.6 per examination), and 47 instances in which agreement or disagreement could not be determined because of an omission in recording by the student or the physician (an average of 1.2 per examination). Of the 63 disagreements, 16 involved a student calling a finding normal that a physician called abnormal. Only two of these 16 were of any clinical importance. The other 47 disagreements involved a student calling a finding abnormal when a physician called the finding normal; practically all of these disagreements occurred because of the student's lack of knowledge of normal variation. The level of competence shown by the students in carrying out physical examinations was judged acceptable.

The final examination at the end of the training program consisted of three parts: the use of simulated patients to assess the competence of the physician extenders in collection of historical data from patients, doing laboratory studies on unknown blood and urine samples, and identification of physical findings and abnormalities from color slide photographs. The historical data, procedures and abnormalities used on the examination were called for in at least one of the 39 algorithms.

Each student interviewed three simulated patients. Each patient simulated a different presenting complaint: joint pain, sore throat or abdominal pain. The students were evaluated on their ability to obtain the required historical information and on their interviewing skills. All students recorded at least 75 percent of the total historical points that should have been collected and all were

judged to be competent interviewers. The laboratory procedures section of the final examination involved carrying out a hematocrit determination on three different blood samples and making a complete analysis (both dipstick and microscopic) on three urine samples. All students satisfactorily carried out at least seven of the nine procedures. The set of 29 color slide photographs showed observable physical findings and abnormalities such as scleral icterus. All students identified at least 75 percent of the slides correctly.

Summary and Conclusions

A 12-week training program for physician extenders was developed around the set of skills required to operate 39 clinical algorithms. In addition to defining a training program, the algorithms were useful in audits to assess student progress and to identify areas where individual students needed additional instruction.

The training program showed a means of relating the education of physician extenders to their subsequent performance on the job. An evaluation of their work in the drop-in clinic has been presented elsewhere.[4] The physician extenders have also functioned well in specialty clinics (for example, in a renal clinic) in which algorithms have been written to guide them in the relevant tasks. In addition, the history-taking and physical examination skills of the physician extenders have been used to collect the defined data base portion of the problem-oriented medical records used in a primary care clinic.

In brief, a relatively short training program based on clinical algorithms provides an interesting alternative to the two-year physician's assistant programs that are modeled on the ways used to train physicians. Initial skepticism notwithstanding,[10] clinical algorithms are proving to be of use in a variety of ways, and additional experiments should be undertaken.

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Who Should Apply Tourniquets?

Tourniquets can be used to advantage by surgeons, but those who are not trained in tourniquet use can do more damage than good. I've seen five patients now who have had tremendous bleeding with a tourniquet in place. We found that pressure suffices in most types of injuries, and we've tried to teach our people not to use tourniquets unless they've been well-trained. Tuffier, a French surgeon in World War I, wrote that all tourniquets should be removed from the medical supplies in ambulances, so it seems that this observation is not new.

—NORMAN RICH, MD, *Washington, DC*
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Special Article

Maternity and Perinatal Services in an Urban-Suburban Area

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The need for community-wide planning of maternity and newborn services is illustrated by a survey of services in Alameda County, California. The decline in birthrate, coupled with the persistence of a number of low volume obstetrical and newborn units, is reflected in generally underutilized and unevenly distributed services. Primary, intermediate and tertiary levels of care are represented, but not always in a logical relationship to community needs. Postgraduate training in obstetrics and gynecology and in pediatrics continues to produce increasing numbers of specialists despite declining fertility and a decline (represented by children and youth) in the total population.

THE STIMULI for changes affecting the American health care "system" are a combination of social, technological, political and economic factors. A partial list of current or anticipated forces contributing to the impetus for changes in the field of maternal and child health includes the following:

- Continuing unfavorable comparison of rates of perinatal morbidity and mortality between the United States and certain other developed countries. The American College of Obstetricians and Gynecologists announced as one of its major goals a reduction by 50 percent in infant mortality to 10 per 1,000 live births in the decade 1973 through 1983.
- The rapidly rising cost of health care.
- The demographic trend toward smaller families and reduced fertility in recent years.
- The anticipation of federal legislation creating some form of national health insurance.
- The maldistribution and malutilization of trained personnel in reproductive medicine and pediatrics.
- Technological advances available in fetal and perinatal medicine, including a plan for regionalized centers for intensive care.
- The increased role of consumers in the evolution of policy regarding health care.
- The "malpractice crisis" currently affecting the practice of medicine.
- The growth of the health team concept, with professionals other than physicians functioning in extended roles in primary health care.

This list could be extended further, but it is sufficient to show the melange of changes contributing to "future shock" among practitioners and consumers alike. Because it is the modification of what exists rather than the creation of a totally new system that we now face, the ap-

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proach will probably be in the recognition that change must take the form of the art of the possible in a free democratic society.

The authors, in cooperation with other Maternal and Child Health (MCH) faculty members of the University of California School of Public Health and the staff of the Alameda County Health Services Agency, recently surveyed the resources for the care of mothers and newborn infants in Alameda County, California. Alameda County has many features that typify the problems to be addressed in attempts to improve the care of mothers and infants. Therefore, it is hoped that the results of this survey will provide a realistic framework for practical planning so that the process of change can be orderly and constructive.

Alameda County, with a population of 1,073,184 in the 1970 census, had an 18.2 percent population increase from 1960 to 1970. A further 13.1 percent increase is expected from 1970 to 1980. Two thirds of the county's population is white, (67.2 percent), 15.0 percent is black, and 12.6 percent is of Spanish surname. Of all families in the county, 8 percent are considered to be in the poverty group. Composite perinatal mortality for 1970 through 1974 included 10.7 fetal and 12.4 neonatal deaths per 1,000 live births, compared with 10.7 and 11.2, respectively, for California as a whole.

Changes in the Live Birth Rate Affecting Alameda County

In the past 25 years the birth rate in Alameda County generally has reflected the demographic trends characteristic of California and the United States as a whole. While the county's live birth rate is consistently lower than those of the state and the nation, it reflects the same progressive downward trend that began in the late 1950's. Data collected in the course of this survey indicate no significant change in the trend to date. Table 1 compares the live birth rate of Alameda County with rates for California and the United States at intervals from 1950 to 1975.

Changes in the Number of Deliveries by Hospital

The pattern of hospital deliveries in Alameda County is significant in the light of growing national interest in planning and providing perinatal services regionally. Table 2 indicates the number of deliveries occurring among the 13 hospitals providing obstetrical service in the county. (A 14th, the United States Naval Hospital, Oakland, provides obstetrical services for armed forces personnel and their dependents, and is not included in this survey.)

TABLE 1.—*Crude Live Birth Rates*

Year	*United States*	*California*	*Alameda County**
1950	23.6	23.3	N.A.
1955	24.6	24.4	23.3
1960	23.7	23.7	23.0
1965	19.4	19.1	18.6
1970	18.4	18.2	17.5
1971	17.3	16.3	15.7
1972	15.6	15.0	13.7
1973	15.0	14.5	12.8
1974	14.9	14.9	13.3
1975	14.8 (prov.)	14.8 (prov.)	13.4 (prov.)

*Excluding Berkeley and Albany.
Sources: Statistician, Alameda County Health Services Agency and Vital Statistics of the United States, Annual reports.

TABLE 2.—*Number of Annual Deliveries in Alameda County by Hospital, 1973 Through 1975*

*Hospital**	*1973*	*1974*	*1975*
1	1,886	2,000	2,144
2	1,874	1,965	1,983
3	1,868	2,010	1,993
4	1,862	1,944	1,876
5	1,039	1,048	1,089
6	956	895	787
7	861	892	903
8	725	656	686
9	702	600	570
10	672	695	763
11	552	492	528
12	421	431	397
13	298	326	302
TOTAL	13,716	13,954	14,021

*Numbers correspond to location on map, Figure 1.

Four of the 13 hospitals have obstetrical caseloads between approximately 1,800 and 2,000 deliveries a year. These are scattered geographically along a roughly north-south axis through the most densely populated areas of the county (see map, Figure 1).

Seven hospital have caseloads between approximately 500 and 1,000 deliveries a year. While two of these serve less densely populated and geographically more isolated areas, the others are in the same general axis and in reasonable proximity to one another or to the four institutions with the county's higher volume services, or to both. The eastern district, which is the high priority health district in terms of health needs, contains no hospital with a large obstetric and newborn service.

Of the two hospitals with less than 500 deliveries a year, one serves a traditionally relatively isolated population on an island separated from

the city of Oakland by an estuary, and the other is near the geographic center of a low income, high density population characterized by the highest infant mortality among the four health districts of the county.

All four of the high volume hospitals had small increases in their total deliveries in 1974 over their 1973 levels. However, these increases (the largest being 7 percent) were generally slight and can hardly be interpreted as reflecting a significant trend toward concentration of maternity care in large volume institutions. A total of six other Alameda County hospitals with modest obstetric caseloads discontinued maternity services between 1955 and 1967, but there has been no further consolidation since then. (Since this survey was completed, one other intermediate volume hospital in Oakland has discontinued its obstetrical service.)

Review of Selected Survey Findings

In the sections to follow, those hospitals with annual deliveries in the 1,500 to 2,000 range will be designated as high volume, those with 500 to 1,500 as intermediate volume and those with less than 500 as low volume institutions.

Staffing

All 13 hospitals have an obstetrics and gynecology staff chaired by a board certified specialist. All but one have a corresponding pediatric staff; three of the four high volume hospitals, and one intermediate hospital have a separate pediatrician in charge of the newborn service in addition to a chairman of pediatrics.

With the exception of the two Kaiser Foundation hospitals, which have full time staffs to serve Kaiser Health Plan patients, these department chairmen are all private practitioners who serve part-time.

Most of the hospitals reported that most deliveries are attended by specialists in obstetrics and gynecology. While the number of general practitioners who include obstetrics in their practices has been declining for a number of years, the current malpractice crisis has accelerated this trend. In today's liability insurance market few physicians other than specialists with a significant obstetrical caseload can afford the increased premiums charged physicians who provide obstetrical services.

Figure 1.—Location of hospitals with maternity units in Alameda County. Numbers correspond to those in Table 2.

Perinatal Mortality Committee

All four of the high volume hospitals conduct a review of perinatal deaths weekly, biweekly or monthly. Two of them are multidisciplinary, with obstetrics, pediatrics, neonatology, anesthesiology and pathology represented. The others are conducted in the form of a joint obstetric-pediatric perinatal review with the other departments not routinely involved.

Among the nine intermediate and low volume hospitals, four had no perinatal mortality committee at the time of the survey. Three had quarterly or monthly perinatal death reviews by representatives of obstetrics and pediatrics, one by the obstetrics department alone, and one (intermediate) included its perinatal death review with the hospital's standing committee review of all hospital deaths. Reports of perinatal mortality committee reviews of individual deaths were not made available for review in this survey.

The county medical association (Alameda-Contra Costa Medical Association), to which a majority of practicing obstetricians and gynecologists and practicing pediatricians belong, conducts an annual perinatal mortality and morbidity survey through its standing Perinatal Mortality Committee. While the county medical association strongly encourages each hospital to have its own perinatal committee, compliance is optional and incomplete—and there is no mechanism to require standard reporting of perinatal events in the annual survey. Consequently, comparisons among the various individual hospitals' perinatal mortality rates is invalidated by differences in reporting criteria.

Despite these shortcoming in documentation, the county medical association's Perinatal Mortality Committee is a potentially useful vehicle for communication among representatives of the various hospitals, an advocate of using standard perinatal review procedures yielding results that can be compared and a multidisciplinary in-house peer review vehicle for physicians in the private medical community concerned with the health care of mothers and newborn infants.

Anesthesiology Service in Maternity Care

Three hospitals (two high volume, one intermediate) provide coverage by a physician anesthesiologist for all deliveries. The remainder, with a single exception, rely on nurse anesthetists, with an anesthesiologist generally available from the surgical operating room for backup service or complicated cases. Only one hospital reported no backup anesthesiology coverage for its nurse anesthetists, but in this institution an anesthesiologist is available for cesarean sections.

In general, anesthesia coverage in delivery rooms appears oriented primarily to care of the mothers. While Apgar scoring is routine (generally at one and five minutes) at all of the hospitals, only two of the 13 report that an anesthesiologist is responsible for the Apgar scoring, and in one of these the anesthesiologist is not present at all deliveries. In most of the hospitals Apgar scoring is done by the attending physician or the delivery room nurse, or both. In five hospitals a nurse anesthetist has this responsibility.

Prenatal Care

Most hospitals surveyed indicated that deliveries occurring with no history of prenatal care were rare or occasional, or not more than 1 or 2 percent of deliveries. Only one hospital reported as high as 10 percent and another hospital 15 percent (estimated) deliveries without prenatal care; both of these were low volume hospitals.

Maternity Beds

A precise tabulation of available maternity beds is no longer possible since most hospitals have abandoned strictly separated maternity wards in favor of flexible arrangements with "swing" beds that may be occupied either by postpartum or clean gynecology cases, depending on daily needs. In general obstetrical bed space in Alameda County hospitals is considerably over-provided and underutilized. Several of the hospitals reported 50 percent or less average occupancy, reflecting the county-wide decline in births in recent years.

Special Maternity Services for High Risk Mothers

Only one hospital (high volume) conducts a special clinic for high risk maternity patients. In this instance all maternity patients are screened at intake according to a locally designed protocol. Those with identified risk factors, approximately 10 percent, are referred to a special prenatal clinic attended by the senior obstetric staff and chief resident, with special consultants and dietary assistance available.

Of the remaining 12 hospitals, only one reported significant identification and transfer of high risk mothers to tertiary care institutions in the area. With this sole exception, the hospitals

generally reported a reluctance by obstetricians to transfer high risk patients before delivery, although high risk newborns are not infrequently transferred to hospitals with special newborn intensive care units in the area.

Fetal Monitoring

Electronic monitoring of labor, both internal and external, is available at all 13 hospitals. In no instance is monitoring routinely done, although seven hospitals reported that it is done in most cases, with varying ratios of external versus internal techniques. In general, obstetricians appear to be withholding judgment on routine monitoring in uncomplicated cases, while there is a consensus on its use in cases involving risk factors.

Newborn Services

As with maternity beds, no instance of crowded or overutilized newborn nursery facilities was encountered among the 13 hospitals surveyed. Several hospitals have considerable unused nursery space which has been closed in recent years.

Of the four high volume hospitals, the two that serve the Kaiser prepaid health care system have their own neonatal intensive care network. The Kaiser Oakland hospital has a fully equipped and staffed neonatal intensive care unit which receives referrals from several other Kaiser hospitals in the area, and which shares a full-time neonatologist with the Kaiser Hayward hospital. The latter, with intermediate intensive care facilities, however, transferred only four of 82 low birth weight babies delivered in 1974. The remaining two high volume private hospitals in the county also have intermediate newborn intensive care facilities and have developed a close working relationship with the neonatal intensive care unit of the Children's Hospital Medical Center of Oakland. The latter, through its transport and educational outreach program, provides in-service training of local hospital nursery staffs, consultation and staff training visits, assignment of neonatal intensive care unit nurses and pediatric residents in rotation, and special neonatal transport service with in-transit intensive care.

During 1974 the Children's Hospital Medical Center unit was responsible for the care of approximately 900 high risk newborns transported from some 30 Northern California hospitals.

In contrast to the underutilization of available newborn nursery facilities in general, the resources in Alameda County for intensive neonatal care have been overtaxed. A report based upon 1972-1973 data indicated an average occupancy rate of 139 percent (range 77 to 160) for the neonatal intensive care units serving the East Bay area which includes Alameda County. This pressure is now being alleviated by the opening of a newly constructed unit at the Children's Hospital Medical Center with a capacity of 20 infants in 1974, and an increase to 40 by July 1976. The medical director of the Children's Hospital Medical Center noted that the specialized training of the neonatal intensive care unit nursing staff was the key item in completing this expansion, since it requires 11 weeks of intensive on-the-job training to prepare each of these nurses for the new responsibilities in the unit. Pending completion of Children's Hospital Medical Center's expansion, several hundred newborns were transported each year to alternate centers in the San Francisco Bay Area. The Children's Hospital Medical Center staff assists in finding an alternate unit when needed, and recently Stanford University Medical Center, in a nearby county, has been designated as one of two Infant Medical Dispatch Centers in California, so that immediate location of alternate neonatal intensive care unit facilities can be made available with minimal delay.

Though pediatricians were found to be generally less resistant to organizing perinatal services regionally than their obstetrical colleagues, both groups preferred selective transfer of high risk neonates. In general, transport of low birth weight infants to a regional neonatal intensive care unit is reserved for those in whom there is evidence of respiratory distress or complications other than prematurity per se. Several informants expressed confidence in their hospitals' ability to provide adequate care for an increasing proportion of low birth weight infants as local equipment and sophistication in the care of these infants grow.

Manpower Considerations

Alameda County does not suffer from the shortage of trained manpower that affects some areas of the United States. A desirable geographic location, pleasant climate, abundance of social, cultural, and recreational resources, and a growing population (increase of 18.2 percent from 1960 to 1970) combine to make it an attractive location for the practice of medicine. It does, however, reflect the uneven distribution typical of combined urban-suburban American commun-

ities with heterogeneous populations, with the heaviest concentration of physicians in the downtown area and suburbs, and with relative scarcity in the rural areas and low-income residential districts.

The 1975 directory of the Alameda-Contra Costa Medical Association listed 115 pediatricians practicing in Alameda County, or a ratio of approximately 1:9,000 population, and 90 specialists in obstetrics and gynecology, a ratio of 1:11,000 population. Comparison with listings in the Directory of American Medical Specialties indicates that virtually all of the Board Certified specialists are represented in the membership of the county medical association.

Therefore, even though not all of the specialists in obstetrics and gynecology are currently practicing obstetrics, it is evident that ample trained personnel exist, if evenly distributed, to afford specialist care to all mothers and infants in the county. Moreover, the growth of residency training both in pediatrics and in obstetrics and gynecology suggests that sufficient specialists in these fields will be produced to more than maintain these ratios in the face of the anticipated 13.1 percent population increase projected for the county between 1970 and 1980. Residency positions in obstetrics and gynecology nationwide increased by 25 percent from 1963 to 1973 and pediatric residency positions more than doubled in the same period.

The role of paramedical personnel in enhancing the efficiency, reducing the cost or compensating for unequal distribution of specialist physicians is not yet sufficiently established to measure in Alameda County. Both maternity and pediatric nurse practitioners have been trained in California training programs for several years, but their place in the health team remained legally uncertain until revision of the California Nurse Practice Act in 1974. Their diffusion into employment by the private medical community, while it has begun, has been slowed by the current apprehension over liability and rising costs of insurance which concern many would-be physician employers. They are, however, being widely and effectively used in a number of hospitals and clinics, both public and independent, and in a few private practices, where their acceptance by patients and physician colleagues has been favorable. It is simply too early to say quantitatively what their ultimate contribution to the health team will be in Alameda County.

The same observation applies even more to nurse-midwifery in California, since the legislation allowing nurse-midwives to attend normal obstetrical cases was enacted only in late 1974.

Only seven of the 90 specialists in obstetrics and gynecology listed were women. Consumer advocates in general, and the feminist movement in particular, have been increasingly vocal in their criticism of male dominated obstetrical care. As opportunities grow for women to pursue careers in the health professions, increased participation of women in maternity care undoubtedly can be expected, whether as physicians, nurse-midwives or nurse-practitioners.

Training New Medical Specialists

Obstetrics and Gynecology

According to data from the American Medical Association, from 1950 through 1962 the number of programs approved for training residents in obstetrics and gynecology in the United States increased. Beginning in 1962 the number of approved residency programs has decreased by a fourth (Table 3).

However, from 1950 through 1973 the number of total positions for residents, and the number of these positions filled has considerably increased.

The percentage of resident positions filled rose from 1950 to 1959, decreased somewhat in 1961, and has been at the level of 86 to 93 percent since 1961 (Table 3).

Pediatrics

From 1950 through 1963 the number of programs approved for residency training in pediatrics increased. Since 1963 the number of approved programs has decreased by a fourth. (Table 4).

However, from 1961 through 1973 the number of total positions for residents and the positions for residents filled has consistently increased.

The percentage of resident positions filled rose from 1950 to 1958, decreased to a lower level from 1959 to 1969, and rose again from 1970 to 1973 (Table 4).

Therefore, an overall summary of the national effort to train medical specialists in obstetrics and gynecology and in pediatrics is that, while the number of approved programs has decreased, the number of persons being prepared has increased. This increase in both obstetrician-gynecologists and in pediatricians has occurred in

TABLE 3.—*Residency Training in Obstetrics and Gynecology in the United States, 1950-1973**

Year	Approved Program	Positions Offered	Positions Filled	Positions Vacant	Percentage Filled
1950	381	1,599	1,266	333	79
1951	406	754	564	190	75
1952	326	616	520	96	84
1953	352	688	589	99	86
1954	374	737	637	100	86
1955	406	839	763	76	91
1956	473	904	800	104	89
1957	484	1,014	942	72	93
1958	477	1,013	956	67	93
1959	446	960	908	52	95
1960	462	942	880	62	93
1961	491	944	844	100	80
1962	483	2,705	2,403	242	91
1963	483	2,728	2,457	271	90
1964	434	2,806	2,500	306	89
1965	402	2,824	2,526	298	89
1966	391	2,829	2,507	322	89
1967	381	2,897	2,526	371	87
1968	358	2,872	2,503	369	87
1969	364	3,042	2,572	470	85
1970	350	3,081	2,655	426	86
1971	346	3,177	2,800	377	88
1972	337	3,368	3,006	362	89
1973	347	3,413	3,183	230	93

*Figures do not include separate residencies in obstetrics or gynecology alone which were available only until 1961.

Source: The American Medical Association's Annual Directories of Approved Internships and Residencies.

TABLE 4.—*Residency Training in Pediatrics in the United States, 1950-1973**

Year	Approved Program	Positions Offered	Positions Filled	Positions Vacant	Percentage Filled
1950	242	1,258	1,073	185	85
1951	237	670	533	137	80
1952	244	639	526	113	82
1953	249	739	634	105	86
1954	246	722	638	84	88
1955	265	738	637	101	86
1956	266	802	715	87	89
1957	281	843	737	106	87
1958	291	934	864	70	93
1959	295	937	838	99	89
1960	309	981	886	95	90
1961	315	1,056	843	213	80
1962	342	2,100	1,735	365	83
1963	356	2,234	1,820	414	81
1964	308	2,290	1,935	355	85
1965	297	2,397	2,043	354	85
1966	289	2,430	2,070	360	85
1967	277	2,508	2,186	322	87
1968	260	2,539	2,185	354	86
1969	250	2,764	2,445	319	89
1970	258	2,830	2,592	238	92
1971	250	3,086	2,844	242	92
1972	251	3,496	3,238	258	93
1973	274	4,409	4,231	178	96

*Figures do not include specialized residencies in pediatric allergy and cardiology.

Source: The American Medical Association's Annual Directories of Approved Internships and Residencies.

spite of the pronounced reduction in the live birth rate, in the fertility rate and in the proportion of the total population represented by children and youth.

California data for 1974 show a beginning reversal in the downward trend in recent years in fertility, prompting demographic analysts to suggest that some women who have postponed marriage and childbearing do not intend to remain childless and may be starting to make up for lost time. Yet, while current projections of population trends for the immediate future include some increase in annual births over the coming decade, these generally do not anticipate a baby boom of a magnitude of that after World War II.

The fact remains that the output of trained medical specialist manpower both in obstetrics and gynecology and in pediatrics has neither corrected the maldistribution of specialists nor allowed for fluctuations in the need for specialists according to demographic trends. As a result of this lack of an overall plan, dislocations and adjustments in patterns of practice, neither planned nor welcomed by the physicians themselves or their patients, are bound to occur. Krassner and Muller, in a recent analysis of manpower trends in obstetrics and gynecology[2] point out that the greatest impact of oversupply will be on new entrants into the specialty of obstetrics and gynecology. They suggest that the reallocation of physician time to allow for the increased need for fertility control will come about through market forces. Ward, in a subsequent comment,[3] emphasizes that nonphysician professionals are now being trained to provide family planning services and suggests instead that rendering primary health care to women is more likely to fill obstetricians' time released by declining births. Whatever the nature of the adjustment, no corresponding compensatory market mechanism appears on the horizon for pediatricians, whose relative oversupply parallels that of obstetricians.

Discussion

The findings of this survey illustrate the need for community planning directed at four specific problems in the care of mothers and newborn infants in Alameda County. These may be summarized as follows:

1. There is need for further consolidation of obstetrical and newborn facilities. Despite general acceptance of the concept of a regional ap-

proach in principle, there has been virtually no consolidation of small obstetrical and newborn units since 1967. (As previously noted, one intermediate volume hospital has discontinued its obstetrical service since this survey was completed.) The resulting underutilization of generally overbuilt hospital maternity and nursery units is costly and inefficient.

Among the general principles for consideration in a possible consolidation are the grouping or regrouping of the smaller maternity services into reasonable geographic service areas, which the various segments of the county community would find acceptable. This might include large urban areas such as the city of Oakland, on the one hand, and other parts of the outlying county which are geographically close to each other and within a reasonable travel time. For example, the maternity services of hospitals within the metropolitan area of Oakland might be consolidated for an overall total of 2,800 annual deliveries, thereby meeting the criteria for a bona fide level II obstetric service.

2. There is need for a comprehensive multidisciplinary program to provide high-risk maternity and neonatal care in the central city area where perinatal and infant morbidity and mortality rates are highest.

Such a program, patterned after successful maternal and infant projects in a number of American cities, should include screening for risk factors and special nutrition, education, social welfare, consultative medical and laboratory resources for those who meet appropriate criteria for intensive prenatal and perinatal care. Special emphasis should be given to care for pregnant teenagers, to provide them with preconceptional care (including health care, health education, family life education and nutrition education and service).

3. There is need for a coordinated plan to assure appropriate geographic distribution of health manpower in the face of

- demographic trends, notably the pronounced reduction in fertility in recent years;
- a relative overproduction of medical specialists;
- continued maldistribution of health personnel, and
- increasing reliance on allied health personnel in the delivery of primary care.

4. There is need for more effective planning and coordination of services provided by public and voluntary community health agencies, professional societies and private practitioners in order to avoid wasteful duplication and oversupply of resources and assure equitable access to quality care in all areas of the county.

Conclusion

The findings of this survey of one urban-suburban community in California have significant implications for similar communities throughout the United States. Similar surveys to identify the strengths, weaknesses and imminent needs of communities throughout the country would be useful in establishing a framework for constructive planning of health delivery systems in the continuing quest for equitable, efficient and high quality health services for *all* families. It is suggested that official health agencies and professional societies take the leadership in these surveys, as a first step toward planning organized, community-wide health care of maternity patients and newborn infants.

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Notes on Alcoholism and Drug Abuse

On Prescribing Medications for Recovering Alcoholic Patients

PRESCRIBING MEDICATION for a patient who is trying to maintain abstinence from alcohol or other habituating or addictive drugs may involve difficult decisions. Recovering alcoholic patients may at some time need medication for sedation, sleep, pain, cough, intestinal symptoms or depression. Many medications used for these symptoms increase the risk of creating a new habituation or addiction. Patients who have shown a dependency to alcohol frequently show a cross dependency to any medication which has the capacity to elevate or depress the patient's mood. In addition, liquid medications that have alcohol as a base should be avoided (a recent check of a local hospital pharmacy showed 87 different liquid medications that contained ethyl alcohol). In several accounts, the use of medicinal alcoholic preparations precipitated a drinking spree in recovering alcoholic patients. If a recovering alcoholic patient is taking disulfiram (Antabuse®) and does not mention it, the disulfiram-alcohol reaction could be unwittingly triggered.

If an emergency occurs making it necessary that such a patient be tranquilized, antihistamines (including diphenhydramine hydrochloride capsules [Benadryl®], hydroxyzine hydrochloride [Atarax®] and hydroxyzine pamoate [Vistaril®]) provide a relatively lower risk of patient dependency than meprobamate, barbiturates or benzodiazepine drugs. Increasing the dosage of an antihistamine is usually satisfactory for inducing sleep.

The most effective analgesics are controlled drugs—these carry an obvious warning of potential patient dependency. A physician should avoid prescribing an analgesic with which the patient has had dependency problems in the past, although this may be unavoidable if emergency treatment is necessary. Short-term, closely supervised treatment is always desirable in such cases. Prescribing a pure analgesic is preferable to prescribing compounds that contain mood elevators or depressants. Methotrimeprazine (Levoprome®), an injectable nonnarcotic analgesic, has been used in hospital with success when treating recovering alcoholics for pain.

For serious coughs codeine in tablet form is recommended. It is important to explain to patients that it is a narcotic. Some patients prefer the idea of a cough syrup. Some cough syrups that do not contain alcohol are Triminacol® cough syrup, resin complexes of hydrocodone and phenyltolxamen (Tussionex®) suspension, Actifed-C® expectorant, Hycodan® syrup and Hycomine syrup®. It should be noted, however, that most cough syrups contain other compounded ingredients which may complicate the situation.

Nausea and vomiting are well controlled by injections, tablets or suppositories of trimethobenzamide hydrochloride (Tigan®) or prochlorperazine (Compazine®). Intestinal spasm is easily relieved by dicyclomine hydrochloride (Bentyl®) tablets or injections. Again, caution should be used to avoid antispasmodic or antiflatulent compounded medications that contain barbituates, tranquilizers or liquid preparations with an alcohol base.

Most liquid prescription medications for diarrhea have an alcohol base. If nonprescription Kaopectate® proves ineffective for diarrhea, diphenoxylate hydrochloride with atropine sulfate (Lomotil®) tablets should be tried. Even though the drug is an exempt narcotic compound, Lomotil® tablets have not proved to have high addicting potential, but certainly no open prescription should be provided. Codeine tablets might also be used for diarrhea symptoms.

Nonpsychotic depression in recovering alcoholic patients is best treated by the involvement of patients in a continuing recovery program such as

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These notes were selected and prepared under the direction of the California Medical Association's Committee on Alcoholism and Other Drug Dependence (1976). In the opinion of the Committee they represent information that has gained acceptance in clinical practice.

When these items were prepared the members of the committee were Arthur Bolter, MD, Chairman; Jack D. Gordon, MD; Stanford Rossiter, MD; Jokichi Takamine, MD; Donald F. Taugher, MD; Jude R. Hayes, MD; Isaac Slaughter, MD; James T. Barter, MD, and John A. Newson, MD.

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Alcoholics Anonymous, continuing alcohol counseling or psychotherapy. If the use of antidepressant medication becomes necessary, the tricyclic drugs (for example, amitriptyline hydrochloride [Elavil®], imipramine hydrochloride [Tofranil®]) seem to be best because they have little potential for physical addiction. In general, the benzodiazepine drugs such as diazepam (Valium®), chlordiazepoxide hydrochloride (Librium®), oxazempam (Serax®), clorazepate dipotassium (Tranxene®), flurazepam hydrochloride (Dalmane®) and drugs containing meprobamate such as Deprol®, which contains meprobamate and benactyzine hydrochloride, have a high potential for dependence and should be avoided for routine outpatient use.

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Propoxyphene-Napsylate (Darvon-N® or PN) in the Treatment of Heroin Dependence

PROPOXYPHENE-NAPSYLATE (PN), a drug chemically similar to methadone, has been shown useful in the management of withdrawal from heroin dependence. It does not completely suppress withdrawal in persons addicted to large amounts of narcotics, but it appears to be adequate for control of the symptoms which occur in those addicted to heroin at the strength common in street use at present. The advantage of PN in the symptomatic management of withdrawal symptoms (such management includes combined use of anticholinergics, hypnotics and muscle relaxants) is that it is usually effective with less of those other medications. Advocates claim that PN produces fewer and less severe side effects such as sedation, constipation and sexual dysfunction, than does methadone. Patients remain free of heroin use following detoxification with PN about as often as when methadone is used in the detoxification process.

However, important risks are associated with the use of propoxyphene, in both the hydrochloride and the napsylate salt forms; large doses taken at one time appear to predispose to convulsions. Because of its convulsive potential and other complications of overdose, particularly in combination with alcohol, prudence would contraindicate prescriptions for addicts of large amounts of PN for unsupervised use. In large doses the napsylate salt is believed to be safer than the hydrochloride salt, probably because it is absorbed more slowly from the intestine.

Long-term toxicity is not known, although continuing clinical use and street use have not yet hinted at serious complications.

There is a significant potential for abuse and an illegal market for both the hydrochloride and the napsylate forms. Although no special security arrangements are required for use of PN, as they are for methadone, care should be taken to guard against the diversion to street use of any propoxyphene prescribed or dispensed. It has appeared in illegal or street traffic and in the urinalysis findings for patients in drug abuse treatment programs, apparently diverted from legal sources.

Apparently, in clinical situations many physicians are at present prescribing the drug at high doses—and at low doses in combination with other target symptom medications—for heroin detoxification. No special federal licensure is required; however, a physician does assume special responsibilities if he uses a dose higher than the manufacturer's recommended dose (100 mg every four hours). The usual PN dosage for detoxification is initially 800 to 1,200 mg a day given in two or more divided doses and tapered to zero over a 5 to 21 day period. Such use might be considered experimental or a use not approved by the Food and Drug Administration (FDA). Consequently a physician should get a specific informed consent. Implied consent to the use of standard medication is assumed when a patient comes to a physician requesting treatment. However, the implied consent does not extend to the use of investigational drugs or to the experimental use of familiar drugs.

About such research, or the use of drugs in investigational ways not described by the manufacturer in the package insert, the following information may be helpful. When the FDA approves a New Drug Application, that drug is approved for marketing and advertising for specific indications. The New Drug Application becomes a contract between FDA and the manufacturer, but the physician is not a party to the contract. He is, therefore, free to use a marketed drug in a manner dictated by standard medical practice. The physician must recognize that if he uses a drug for indications not approved by the FDA, or in doses larger than those recommended in the FDA-monitored package insert, he is probably not complying with the national medical community's

standard of practice. The physician then assumes obligations that devolve upon the prescriber when a drug is used in a research situation. (In California, a physician who is providing nominal or actual medical authority for an addiction treatment program which employs drugs for investigational use, as defined here, should insist that the program seek approval from the Research Advisory Panel, Attorney General's Office, State of California.*)

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Laboratory Tests to Detect Drugs of Abuse

PHYSICIANS PLAY a central role in the treatment of significant drug abuse. In order to combat the manipulation and denial that drug abusing patients often employ, physicians must have access to sensitive, accurate and inexpensive laboratory tests with which continued drug use or compliance with treatment can be monitored. Such tests are now widely available at reasonable cost.

The most commonly used procedure is the screening of urine specimens with thin layer chromatography (TLC) and confirmation of positive or negative results by ancillary techniques. The TLC screening technique can detect opiates including the morphine metabolite of heroin, propoxyphene hydrochloride (Darvon®), glutethimide and amphetamines—all to the sensitivity of 1 to 2 μg per ml of urine.

To interpret the results properly, a physician must be aware of the metabolism of the major drugs of abuse. He must also assure himself that the specimen analyzed in fact came from the patient at the purported time of collection. The patient should be personally supervised during the collection of the urine specimen.

For a small additional fee, laboratories will analyze a urine specimen for metabolites of the benzodiazepines (diazepam [Valium®], chlordiazepoxide hydrochloride [Librium®], oxazempam [Serax®], clorazepate dipotassium [Tranxene®]) which appear to be rapidly becoming major drugs of abuse. Sensitive and accurate tests for alcohol have been available for many years and physicians should remain aware that alcoholism frequently accompanies other forms of drug abuse. Alcoholics are often polydrug abusers and may ingest alcohol as a cover for other drugs. Physicians who treat drug abusers must be familiar with the effects of various blood and urine alcohol levels, and interactions of drugs with various alcohol levels.

Inexpensive screening methods are not available for the tricyclic antidepressants which have gained some popularity among drug abusers.

Monitoring the abuser of prescribed drugs presents a more formidable problem to a physician because a battery of tests may be necessary which would be prohibitively expensive to carry out on a regular basis. The more complex gas chromatographic procedures are required for the analysis of drugs such as ethchloruynol (Placidyl®) and methyprylon (Noludar®). However, in a case of medical drug abuse a physician can rely on his clinical judgment and information; that is, observed impairment and information from friends and relatives of the patient.

Laboratories which do these screening procedures in large volume will supply a physician with aids to interpretation as well as current information on patterns of drug abuse observed in their analyses.

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Nonmedical Detoxification of Alcoholic Patients

WITHDRAWAL FROM ALCOHOL without the use of sedative drugs in a home-like facility, supervised by carefully trained personnel (many of whom are recovered alcoholics), is called "the social treatment model." This approach provides a reassuring therapeutic environment where plans for continuing therapy are made, even during the initial phases, and consistently emphasized as an integral part of the treatment. Average length of stay is 3½ days at a cost of about $30 a patient per day—a fraction of the cost of a general hospital stay of similar length.

The requirements for successful nonmedical detoxification are (1) an atmosphere of empathy

*Personal communication from Frederick H. Meyers, MD.

and understanding, (2) carefully selected and trained personnel experienced in assisting and encouraging patients to take the responsibility for achieving recovery, (3) exclusion of the dangerously sick or injured and (4) immediate availability of medical facilities when required.

In 1970 the Addiction Research Foundation in Toronto started the first treatment units based on this social-setting model. About 50,000 patients were admitted initially to the 19 units. Only 5 percent of these were referred to a hospital during the withdrawal period. The rest successfully completed detoxification *without the use of drugs,* relying entirely on the therapeutic environment and skillful management by the staff.

In a recent study of a similar unit in San Francisco, 99 alcoholic patients, chosen randomly from a population of approximately 500, were given careful physical examinations at 24, 48 and 72 hours—33 in each group. Of the 99 examined only four may have been inappropriately admitted to a nonmedical facility because of the severity of accompanying ailments such as heart disease or liver disease. However, even these four patients completed detoxification without difficulty.

Because of the economy and apparent efficiency of this method, it should be considered a principal resource for the detoxification of many alcoholic patients.

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Phencyclidine (PCP) Abuse

PHENCYCLIDINE (PCP) or 1- (1-phencyclohexyl) piperidine first appeared as a street drug in 1967. Because of unpleasant experiences, the drug soon developed a questionable reputation. It was originally developed as a surgical anesthetic, but because of the adverse side effects—patients reported extreme agitation, disorientation, delirium and hallucinations—all human clinical investigations were discontinued.

Despite its early negative reputation, PCP has become a major drug of abuse with a new generation of drug users. Much of the available PCP on the illicit market is sold as something else (tetrahydrocannabinol [THC] or lysergic acid diethylamide [LSD]); however, conscious use of PCP represents the main part of current use. It is called a variety of exotic names such as crystal, angel dust, peace, peace weed, and superweed.

PCP may be ingested in tablet form, sniffed as a powder or smoked in a rolled cigarette prepared by adding crystalline or liquid phencyclidine to parsley or marijuana. The effect will vary with the method of administration; overdosage is much more likely with oral ingestion. Inhalation gives a rapid effect and intoxication tends to be self-limited when PCP is smoked.

Some commonly reported reactions include body image disturbances, depersonalization, perceptual distortions, and extreme feelings of apathy and indifference. The effects of acute intoxication will depend on dosage and route of administration.

The "low dose" state is characterized by mild agitation and excitement, gross incoordination with possible catatonic rigidity exhibited. Horizontal and vertical nystagmus is present with loss of pin prick response.

The "moderate dose" state is marked by coma or stupor with associated hypertension and nystagmus, but no respiratory depression.

"High dose" states are usually the result of oral ingestion and may manifest generalized seizure activity as an added clinical feature.

The most important signs to look for when diagnosing possible phencyclidine intoxication are the presence of vertical and horizontal nystagmus, associated with hypertension in a patient who is acutely confused or comatose, but without evidence of respiratory depression (unless the patient has taken a respiratory depressant also).

An acutely confused patient is best managed by complete sensory isolation with only observation of vital signs. There should be no physical contact nor any attempt to talk the patient down. The general principles of management of coma apply to "high dose" intoxicated states. Gastric lavage or aspiration is indicated in oral ingestion. Diazepam (Valium®) has been used intravenously in the control of seizure activity, and orally for the agitated confused patient if necessary to prevent injury to the patient and others.

ARTHUR BOLTER, MD

REFERENCES

Burns RS, Lerner SE, Corrado R, et al: Phencyclidine—States of acute intoxication and fatalities. West J Med 123:345-349, Nov 1975

Tong TG, Benowitz NL, Becker CE, et al: Phencyclidine poisoning. JAMA 234:512-513, Nov 3, 1975

PCP Revisited. PharmChem Newsletter, Vol 4, Nov 1975

Refer to: Food and Drug Administration: Text of required patient information for IUD's (Information). West J Med 127: 81-83, Jul 1977

Information

Text of Required Patient Information for IUD's

Editor's Note: Effective November 7, 1977, new regulations established by the Food and Drug Administration will require manufacturers of intrauterine birth control devices (IUD's) to print patient brochures describing the uses and possible risks associated with IUD's. The manufacturers must ensure that enough of these brochures are produced to make them readily available in clinics, physicians' offices and health facilities. Under the regulations, physicians must give women an opportunity to read a copy of the brochure and ask questions before deciding to have an IUD inserted. The following is the text that the brochures will use, as published in the Federal Register *on May 10, 1977.*

Patient Information

THIS BROCHURE provides information on the use of intrauterine contraceptive devices (IUD's). There are other birth control methods that may be suitable. Before deciding which type of birth control method to use, you should read this brochure and have the opportunity to discuss fully with your doctor any questions you may have about the IUD and other methods of contraception.

Preinsertion Information—What You Should Know About the IUD

IUD's are small articles of various sizes and shapes which are inserted into the uterus (womb). The purpose of the IUD is to prevent pregnancy.

How the IUD prevents pregnancy is not completely understood. Several theories have been suggested. IUD's seem to interfere in some manner with the implantation of the fertilized egg in the lining of the uterine cavity. The IUD does not prevent ovulation.

The effectiveness of the IUD is measured by the pregnancy rate of women who use it and the rate of adverse reactions and side effects requiring removal of the IUD.

Use-Effectiveness

Different pregnancy and adverse reaction rates have been reported with the use of different IUD's. Because these rates are usually derived from separate studies conducted by different investigators in several population groups, they cannot be compared with precision.

In clinical trials with (__ name of IUD __) _____ patients completed _____ cycles or months in use. The incidence of unplanned pregnancies was _____ per 100 women years or _____ women out of 100 became pregnant in a year while using an IUD. The incidence of adverse reactions requiring medical removal of the IUD is _____ per 100 woman years or _____ women out of 100 discontinued using the IUD for medical reasons.

What You Should Tell Your Doctor

Before you have an IUD inserted, you should tell your doctor if you have ever had, or suspect you have ever had, any of the following conditions which might make the IUD unsuitable as a method of contraception for you:

Abnormalities of the uterus (womb); Allergy to copper; Anemia; Bleeding between periods; Cancer of the uterus (womb) or cervix; Fainting attacks; Heart disease; Heart murmur; Heavy menstrual flow; Infection of the uterus (womb) or cervix; Pelvic infection (pus in the fallopian tubes); Prior IUD use; Prior uterine surgery; Recent abortion or miscarriage; Recent pregnancy; Severe menstrual cramps; Suspected or possible pregnancy; Suspicious or abnormal "Pap" smear; Unexplained genital bleeding; Vaginal discharge or infection; Venereal disease; Wilson's disease.

Adverse Reactions

The following adverse reactions and side effects have been reported and may occur after the IUD is inserted:

Anemia; Backache; Blood poisoning (septicemia); Bowel obstruction; Cervical infection; Complete or partial expulsion; Cysts on ovaries and tubes; Delayed menstruation; Difficult re-

moval; Embedment; Fainting at the time of insertion or removal; Fragmentation; Intermenstrual spotting; Internal abdominal adhesions; Pain and cramps; Painful intercourse; Pelvic infection; Perforation of the uterus (womb) or cervix; Pregnancy; Pregnancy outside the uterus (womb) (tubal or ovarian); Prolonged or heavy menstrual flow; Septic abortion (infected miscarriage) followed in some cases by blood poisoning (septicemia) which can lead to death; Spontaneous abortion (miscarriage); Vaginal discharge and infection.

If you decide on the IUD as your method of birth control, read the following information and instructions carefully. Please keep this brochure so that you may refer to it. If you have any questions, consult your doctor.

Postinsertion Information Description (To Be Supplied by Manufacturer)

Description shall include the following information:

1. Proprietary or established name of the IUD; 2. Model; 3. Physical dimensions (size and shape); 4. Composition (metal or plastic); 5. Color and number of the tail or threads; 6. Other characteristics.

Directions for Use

1. *Checking your IUD.* A tail or thread is attached to the IUD so you can check to see if it is still in place since the IUD can come out of the uterus (womb) without your knowing it. This occurs most often during or right after a menstrual period.

Follow these steps to make sure your IUD is in place:

(a) Wash your hands; (b) Assume the squatting position or seat yourself on the toilet; (c) Insert the index or middle finger high in vagina and locate the cervix (mouth of the uterus [womb]). The cervix feels firm like the tip of your nose; (d) Feel for the tail or thread of the IUD which should be in the cervix high in your vagina; (e) If you can feel the tail or thread it is likely that the IUD is in place and working. You should not pull on the tail or thread. This may displace the IUD; (f) After each menstrual period, you should check to make sure the tail or thread is in place in the cervix. You may check for the tail or thread more often if you wish; (g) If you think the IUD has come out or has been displaced (e.g., you cannot feel the tail or thread or you can feel the IUD itself), use another birth control method, such as contraceptive vaginal foam, cream, or jelly, or condoms (rubbers), until you can be checked. (These alternative methods are not as effective as the IUD.) Call your doctor for an examination; (h) You should return to see your doctor as soon as possible after your next menstrual period, after insertion of your IUD, but no later than 3 months after insertion. This will allow the doctor to make sure that the IUD is in the correct position; (i) After your first checkup, you should be checked at least once a year by your doctor.

2. *Continuation and removal.* While you are wearing the IUD, you may use tampons and take douches, if this is your usual practice. With some IUD's, you may wear the IUD until you wish to become pregnant. With other IUD's it is necessary that they be replaced every year or so in order for you to continue being protected against pregnancy. Check with your doctor concerning this. You should return to your doctor if you wish to have the IUD removed.

Side Effects

The following may occur during or after the IUD is inserted:

(1) Some bleeding occurs following insertion in most women. Because of this, your doctor may choose to insert your IUD during or at the end of your menstrual period. This also reduces the possibility that you are pregnant at the time of IUD insertion. (2) Bleeding between menstrual periods, usually in the form of spotting, may occur during the first 2 or 3 months after insertion. The first few menstrual periods after the insertion may be heavier and longer. If these conditions continue for longer than 2 or 3 months, consult your doctor. (3) Pain, usually in the form of uterine cramps or low backache, may occur at the time of insertion and last for a few days. Simple pain medication usually relieves the cramping. (4) Fainting may occur at the time of insertion or removal of an IUD. This passes quickly and is not usually serious. (5) The IUD may be expelled during the first two or three menstrual cycles following insertion. Expulsion increases the risk of an unplanned pregnancy. Although not as effective as the IUD, the use of a second contraceptive method, such as a contraceptive vaginal foam, cream, or jelly, or condoms (rubbers) is recommended.

Warnings

1. Call your doctor for any of the following reasons:

(a) *Severe or prolonged bleeding.* If the flow is heavier and lasts much longer than your usual menstrual flow, you may need to have the IUD removed to prevent the development of anemia. (b) *Pelvic pain and cramps.* This could mean an infection has developed requiring treatment. (c) *Exposure to venereal disease* (VD). If exposure to venereal disease is suspected, report for examination and treatment promptly. Failure to do so could result in serious pelvic infection because use of an IUD in itself does not prevent venereal disease. (d) *Tail or thread disappearance.* If you cannot feel the tail or thread coming through the cervix, it is possible that the IUD has been expelled or displaced or that perforation has occurred. If any of these has occurred, you are no longer protected from becoming pregnant. Use another birth control method, such as contraceptive vaginal foam, cream, or jelly, or condoms (rubbers) until you can be checked. (These alternative methods are not as effective as the IUD.)

2. Do not undergo medical diathermy (including shortwave or microwave treatments to the abdomen or lower back areas if you are wearing a metal IUD. These treatments may cause heat injury to the surrounding tissue.

Special Warning About Pregnancy with an IUD in Place

Some women become pregnant while using an IUD. If you miss your menstrual period, or if you have a scanty flow during your period, or if you suspect that you might be pregnant, see your doctor right away. Serious complication of sepsis (severe infection), septic abortion (infected miscarriage), and death have occurred when a pregnancy continues with an IUD in place. Most of the occurrences of these serious complications have been reported in the middle third of pregnancy.

If your doctor confirms that you are pregnant, he should remove the IUD if the tail is visible. Removal of an IUD in pregnancy decreases the likelihood of serious complications.

If removal of your IUD proves to be difficult, you and your doctor should discuss at that time the question of continuing the pregnancy in view of the serious complications that may occur. In reaching a decision as to whether or not to have an abortion, it should be remembered that the risks associated with terminating a pregnancy increase with the length of time you are pregnant.

Treatment for Venous Thrombosis

What treatment is indicated for a patient with venous thrombosis?

If a patient is up and walking about, the clot that is in the venous system tends to occlude the lumen. The clot itself is wider, it is shorter and one would have then a blockage at this particular point. Put this patient in bed and . . . the clot . . . becomes longer, it becomes thinner and it becomes nonobstructive. And the blood can flow past, and edema and swelling do not result. This is why one of the standard treatments is still to put these patients in bed as soon as symptoms of venous thrombosis develop.

—H. JAMES DAY, MD, *Philadelphia*
Extracted from *Audio-Digest Family Practice,* Vol. 24, No. 34, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

in memoriam

Baxter, Philip Norman, Oakland. Died May 15, 1977 in Piedmont of heart disease, aged 72. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1934. Licensed in California in 1934. Dr. Baxter was a retired member of the Alameda-Contra Costa Medical Association.

Cook, Enos Paul, San Jose. Died May 18, 1977 in Walnut Creek, aged 87. Graduate of the University of California Medical School, Berkeley-San Francisco, 1916. Licensed in California in 1916. Dr. Cook was a retired member of the Santa Clara County Medical Society.

Cookinham, Franklin Hillman, San Francisco. Died May 9, 1977 in San Francisco, aged 95. Graduate of the Hahnemann Medical College and Hospital, Chicago, 1906. Licensed in California in 1915. Dr. Cookinham was a retired member of the San Francisco Medical Society.

Frazier, Frank F., Bell Gardens. Died October 18, 1976 in Vernon of heart disease, aged 70. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1933. Licensed in California in 1934. Dr. Frazier was a member of the Los Angeles County Medical Association.

Gradow, Alexander, San Francisco. Died May 9, 1977 in San Francisco, aged 79. Graduate of First Moscow Medical Institute, Moscow, R.S.F.S.R., 1926. Licensed in California in 1939. Dr. Gradow was a retired member of the San Francisco Medical Society.

Greenfield, Leonard C., Chula Vista. Died April 24, 1977 in San Diego of heart disease, aged 58. Graduate of the University of Illinois College of Medicine, Chicago, 1942. Licensed in California in 1945. Dr. Greenfield was a member of the San Diego County Medical Society.

Grimmer, Roy D., Covina. Died May 3, 1977, aged 64. Graduate of McGill University Faculty of Medicine, Montreal, 1940. Licensed in California in 1948. Dr. Grimmer was a member of the Los Angeles County Medical Association.

Homer, Ralph William, Ojai. Died May 5, 1977 in Ventura, aged 90. Graduate of the University of California Medical School, Berkeley-San Francisco, 1911. Licensed in California in 1911. Dr. Homer was a retired member of the Ventura County Medical Society.

Levin, Manuel, Fresno. Died May 11, 1977 in Fresno, aged 61. Graduate of the University of Michigan Medical School, Ann Arbor, 1940. Licensed in California in 1950. Dr. Levin was a member of the Fresno-Madera Medical Society.

Lewis, Leon, Martinez. Died May 8, 1977 in Kensington of cerebrovascular disease, aged 72. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1929. Licensed in California in 1930. Dr. Lewis was an associate member of the Alameda-Contra Costa Medical Association.

Loveseth, Leonard Jerome, Millbrae. Died May 7, 1977 in Millbrae, aged 58. Graduate of the University of Alberta Faculty of Medicine, Edmonton, 1943. Licensed in California in 1948. Dr. Loveseth was a member of the San Mateo County Medical Society.

Mathews, Benton Dunnegan, San Francisco. Died May 16, 1977 in Ross, aged 65. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1937. Licensed in California in 1937. Dr. Mathews was a member of the San Francisco Medical Society.

Medicus, Marion E., Beverly Hills. Died May 15, 1977, aged 61. Graduate of the Medical College of Pennsylvania, Philadelphia, 1941. Licensed in California in 1942. Dr. Medicus was a member of the Los Angeles County Medical Association.

Mercado, Pablo A., Walnut Creek. Died May 22, 1977 in Walnut Creek of heart disease, aged 35. Graduate of the University School of Medicine, Mexico City, 1969. Licensed in California in 1973. Dr. Mercado was a member of the Alameda-Contra Costa Medical Association.

Merrill, H. Ross, Hillcrest. Died May 17, 1977, aged 57. Graduate of Northwestern University Medical School, Chicago, 1944. Licensed in California in 1945. Dr. Merrill was a member of the San Diego County Medical Society.

Mounce, Stanley Henry, Long Beach. Died October 20, 1976 in Gardena of heart disease, aged 58. Graduate of St. Louis University School of Medicine, 1948. Licensed in California in 1953. Dr. Mounce was a member of the Los Angeles County Medical Association.

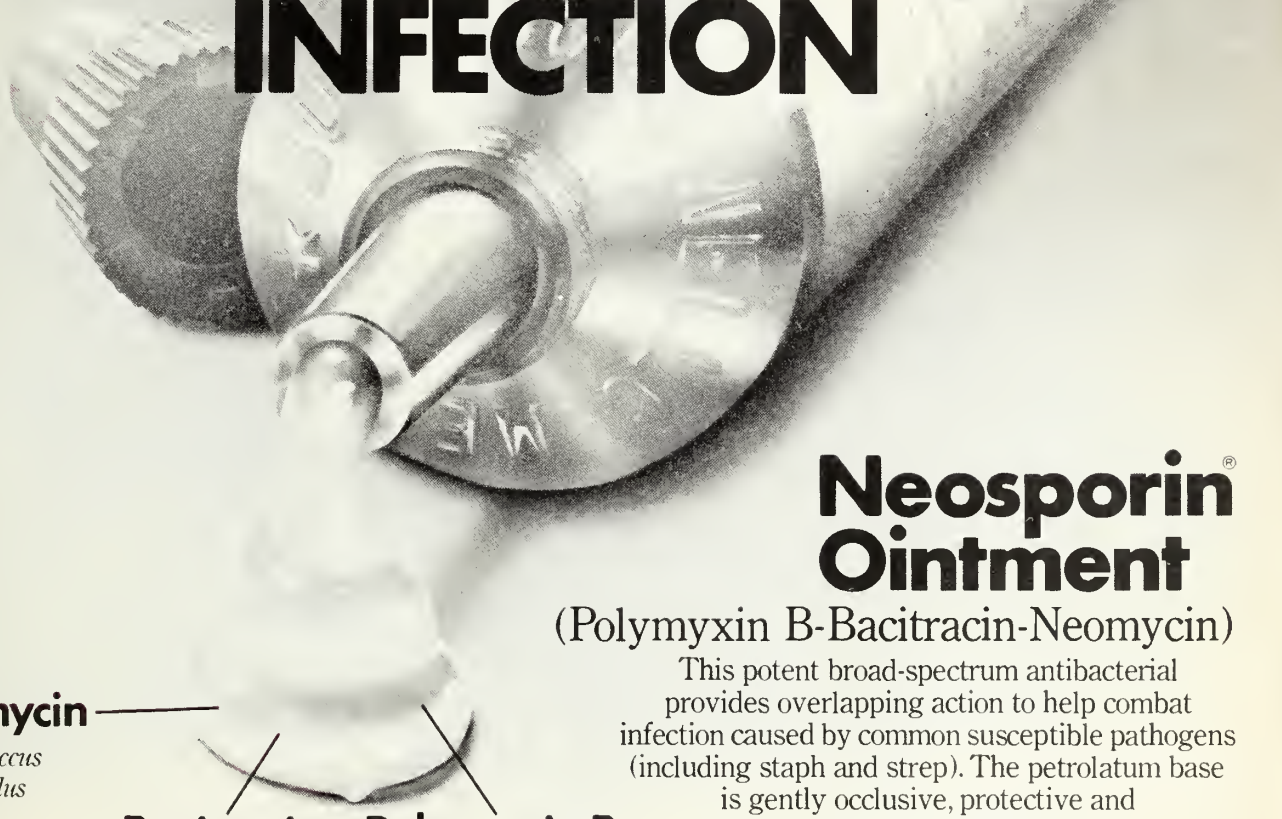
Rickard, Robert N., Oakhurst. Died May 2, 1977 in Oakhurst, aged 61. Graduate of New York Medical College, Flower and Fifth Avenue Hospitals, New York City, 1943. Licensed in California in 1945. Dr. Rickard was a member of the Los Angeles County Medical Association.

Shook, Thomas Raymond, Econdido. Died May 10, 1977 in Escondido, aged 45. Graduate of the University of California, Irvine, California College of Medicine, 1963. Licensed in California in 1964. Dr. Shook was a member of the San Diego County Medical Society.

Sutherland, Richard Lee, Oakland. Died May 22, 1977 in San Francisco, aged 64. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1940. Licensed in California in 1948. Dr. Sutherland was a member of the Alameda-Contra Costa Medical Association.

Wulff, Verna (Verna Wulff Movius), Porterville. Died April 18, 1977 in Porterville, aged 53. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1948. Licensed in California in 1949. Dr. Wulff was a member of the Tulare County Medical Society.

THREE-IN-ONE THERAPY AGAINST TOPICAL INFECTION



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h gram contains: Aerosporin® brand Polymyxin B ate 5,000 units; zinc bacitracin 400 units; neomycin ate 5 mg (equivalent to 3.5 mg neomycin base); cial white petrolatum qs; in tubes of 1 oz and 1/2 oz 1/32 oz (approx.) foil packets.

RNING: Because of the potential hazard of nephro- city and ototoxicity due to neomycin, care should be cised when using this product in treating extensive ns, trophic ulceration and other extensive conditions re absorption of neomycin is possible. In burns re more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML.

consider the effect on coexisting diabetes when you prescribe a vasodilator*

(POSTERIOR VIEW OF PANCREA

no interference in the management of the diabetic patient has been reported with

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the compatible vasodilator TABLETS, 20 mg.

***Indications:** Based on a review of this drug by the National Academy of Sciences National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.

Final classification of the less-than-effective indications requires further investigation.

Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg. Vasodilan injection, isoxsuprine HCl, 5 mg., per ml.

Dosage and Administration: Oral: 10 to 20 mg., three or four times daily. Intramuscular: 5 to 10 mg. (1 or 2 ml.) two or three times daily. Intramuscular administration may be used initially in severe or acute conditions.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartu or in the presence of arterial bleeding.

Parenteral administration is not recommended in the presence of hypotension or tachycardia.

Intravenous administration should not be given because of increased likelihood of side effects.

Adverse Reactions: On rare occasions oral administration of the drug has been associated in time with the occurrence of hypotension, tachycardia, nausea, vomiting, dizziness, abdominal distress, and severe rash. If rash appears the drug should be discontinued.

Although available evidence suggests a temporal association of these reactions with isoxsuprine, a causal relationship can be neither confirmed nor refuted.

Administration of single dose of 10 mg. intramuscularly may result in hypotension an tachycardia. These symptoms are more pronounced in higher doses. For these reasor single intramuscular doses exceeding 10 mg. are not recommended. Repeated administration of 5 to 10 mg. intramuscularly at suitable intervals may be employed.

Supplied: Tablets, 10 mg., bottles of 100, 1000, 5000 and Unit Dose, Tablets, 20 mg bottles of 100, 500, 1000, 5000 and Unit Dose; Injection, 10 mg. per 2 ml. ampul, bo six 2 ml. ampuls. U.S. Pat. No. 3,056

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CONTINUING MEDICAL EDUCATION

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THIS LISTING of continuing education programs in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 146. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

CANCER

August 10—**G. I. Carcinoma.** LLU. Wednesday. 4 hrs. $25.

September 17—**Clinical Implications of New Diagnostic Techniques—Ultrasound, Cat Scan, Radioisotopes, Clinical Chemistry.** San Francisco Regional Tumor Foundation at Fireman Fund Building, San Francisco. Saturday. 4 hrs. Contact: Norma Schlager, PhD, S.F. Regional Tumor Foundation, 14th and Lake, San Francisco 94118. (415) 221-2132.

October 3-7—**Medical Oncology Review.** American College of Physicians and Huntington Memorial Hospital at Huntington Sheraton Hotel, Pasadena. Monday-Friday. 36 hrs. $140, ACP members; $200, nonmembers. Contact: Arlene Ellis, Coord., Med. Staff Affairs, Huntington Mem. Hosp., 100 Congress St., Pasadena 91105. (213) 440-5176.

November 18-19—**Endocrine Aspects of Cancer: New Perspectives.** Mt. Zion Hospital and Medical Center, San Francisco. Friday-Saturday. Contact: Ann Raisbeck, Dept. of Med. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2401.

MEDICINE

September 7-11—**Medical Knowledge Self-Assessment Program Course.** American College of Physicians at Golden Gateway Holiday Inn, San Francisco. Wednesday-Sunday. 30 hrs. $140, ACP members; $200, nonmembers. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

September 9-10—**Skin Flap.** UCSF. Friday-Saturday.

September 14-16—**Pediatric Dermatology.** STAN. Wednesday-Friday. 23 hrs. $225.

September 26-30—**Medical Knowledge Self-Assessment Program Course.** American College of Physicians at Hilton Hotel, Los Angeles. Monday-Friday. 30 hrs. $140, ACP members; $200, nonmembers. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

September 29-30—**Annual Physician Postgraduate Symposium on Heart Disease.** San Francisco Heart Assn. and Council on Atherosclerosis, American Heart Assn., at Golden Gateway Holiday Inn, San Francisco. Thursday-Friday. Contact: Molly Austin, Assoc. Dir., S.F. Heart Assn., 421 Powell, San Francisco 94102. (415) 433-2273.

September 29-30—**Clinical Immunology/Rheumatology Update.** UCSF. Thursday-Friday.

October 1-8—**Cardiology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

October 3-7—**Medical Oncology Review.** See Cancer, October 3-7.

October 5—**Digitalis: New Insights at the Bicentennial.** L. A. Society of Internal Medicine at L.A. Co. Med. Assn., Los Angeles. Wednesday. 1½ hrs. $7.50 for dinner. Contact: Thomas T. Yoshikawa, MD, LASIM, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

October 5-6—**American Heart Association, Greater Los Angeles Affiliate—45th Annual Fall Symposium and 10th Annual Griffith Lecture.** Hilton Hotel, Los Angeles. Wednesday-Thursday. 12 hrs. $65, member of any Heart Assn.; $85, nonmember. Contact: LaVerna Titus, AHA, Greater L.A. Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

October 6-7—**Pediatric Nephrology.** UCSF. Thursday-Friday.

October 7-8—**Techniques for Dermatologic Research in the Office.** UCSF. Friday-Saturday.

October 7-8—**Practical Dermatopathology.** STAN. Friday-Saturday. 16 hrs. $150; $100, residents and those in training. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Med. Ctr., Stanford 94305. (415) 497-6101.

(Continued on Page 24)

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

(Continued from Page 23)

October 8-15—**Endocrinology/Nephrology Review.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

October 10-14—**Practical Electro-Cardiography.** Memorial Hospital Medical Center of Long Beach-UCI at Hotel Inter-Continental, Maui, Hawaii. Monday-Friday. $150. Contact: Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 11-14—**Electrocardiography: Core Curriculum and Self-Assessment.** PMC at Golden Gateway Holiday Inn, San Francisco. Tuesday-Friday.

October 21-22—**Diabetes.** STAN and Santa Clara County Diabetes Society. Friday-Saturday.

October 21-22—**Internal Medicine Symposium—22nd Annual.** Southern Calif. Permanente Medical Group at Hilton Hotel, Pasadena. Friday-Saturday. Contact: Shirley Gach, So. Calif. Permanente Med. Grp., 4900 Sunset Blvd., Rm. 6014, Los Angeles 90027. (213) 667-4241.

October 21-23—**Practical Cardiology—1977.** American College of Cardiology at Del Monte Hyatt Hotel, Monterey. Friday-Sunday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Division of Continuing Education, ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

October 26—**Consultations in Hypertensions.** UCSD at Vacation Village, San Diego. Wednesday.

November 3-6—**California Society of Internal Medicine—Annual Meeting.** Canyon Hotel, Palm Springs. Thursday-Sunday. Contact: CSIM, 703 Market St., Suite 1412, San Francisco 94103. (415) 362-1548.

November 4-5—**Mechanisms of Hemostasis and Thrombosis: Experimental and Clinical Perspectives.** PMC at Fairmont Hotel, San Francisco. Friday-Saturday.

November 7-11—**Pediatric Allergy and Clinical Immunology.** UCSF. Monday-Friday.

November 7-16—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. 10 days. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Division of Continuing Education, ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

November 9—**Endocrinology Seminar.** LLU. Wednesday. 4 hrs. $25.

November 26-December 3—**Lymphoproliferative Disorders.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

December 1-3—**Infectious Disease.** UCSD at Hilton Inn, San Diego. Thursday-Saturday.

December 2-4—**Advances in Heart Disease—1978.** American College of Cardiology at Fairmont Hotel, San Francisco. Friday-Sunday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Division of Continuing Education, ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

December 7—**Lyman A. Brewer III Cardiothoracic Symposium—3rd Annual.** LLU at Hilton Hotel, Los Angeles. Wednesday. 8 hrs. $50.

December 10—**Pulmonary Artery Catheters and Ventilators.** PMC. Saturday. 6 hrs. $300.

OBSTETRICS AND GYNECOLOGY

August 6-8—**Comprehensive Laparoscopy.** UCSD at Sea Lodge, San Diego. Saturday-Monday.

August 27-September 2—**Edward Tyler Symposium on the Practical Management of the Infertile Couple.** Tyler Medical Clinic, Los Angeles, and Univ. of Hawaii School of Medicine at Royal Lahaina Hotel, Maui, Hawaii. One week. 16 hrs. $125. Contact: Exclusive Travel, 3345 Wilshire Blvd., Los Angeles 90010.

October 12-16—**Pacific Coast Fertility Society—Annual Meeting.** Canyon Hotel, Palm Springs. Wednesday-Sunday. 21 hrs. $15, member; $25, nonmember. Contact: Ronald S. Swerdloff, MD, PCFS, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

October 14-15—**Office Gynecology Workshop.** PMC. Friday-Saturday.

October 28—**Advances in Obstetrics and Gynecology—11th Annual Meeting.** Northern Calif. Obstetrical and Gynecological Society at Red Lion Motor Inn, Sacramento. Friday. 7 hrs. Contact: Benjamin J. Berry, MD, Prog. Chr., NCOGS, 3720 Mission Ave., Carmichael 95608. (916) 481-5401.

November 10-12—**Medical Complications of Obstetrics and Gynecology—Annual Fall Seminar in Obstetrics and Gynecology.** UCSF at Mark Hopkins Hotel, San Francisco. Thursday-Saturday.

November 12-14—**Comprehensive Laparoscopy: Current Principles and Practice.** UCSD at Kona Kai Club, Kona, Hawaii. Saturday-Monday.

November 12-19—**Workshops in High Risk Pregnancy: Infertility.** UCSF at Royal Lahania Hotel, Maui, Hawaii. One week.

PEDIATRICS

September 14-16—**Pediatric Dermatology.** See Medicine, September 14-16.

September 15-16—**Pediatric Urology.** See Surgery, September 15-16.

September 28-29—**Brennemann Memorial Lectures—34th Annual.** L.A. Pediatric Society at Bonaventure Hotel, Los Angeles. Wednesday-Thursday. Contact: Eve Black, Exec. Sec., LAPS, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

October 6-7—**Pediatric Nephrology.** See Medicine, October 6-7.

October 15-22—**Pediatrics for the Practitioner.** Children's Hospital of Long Beach and American Academy of Pediatrics, Chapter 2, at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. Contact: Margaret Frederick, Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 21-22—**Adolescent Sexuality and Related Problems.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday.

November 4-5—**Children's Experiences of Health and Illness.** UCD at Claremont Hotel, Berkeley. Friday-Saturday.

November 7-11—**Pediatric Allergy and Clinical Immunology.** See Medicine, November 7-11.

December 3—**Practical Aspects of Sports Medicine for Pediatricians.** American Academy of Pediatrics, Calif. Chapter II Dist. 1X, at Union Square Holiday Inn, San Francisco. Saturday. Contact: Martin Gershman, MD, 595 Buckingham Way, San Francisco 94132.

PSYCHIATRY

September 24-25—**Drug Abuse (Psychopharmacology).** UCLA Saturday-Sunday. 14 hrs. $140.

October 1-2—**Stress Management and Approaches to Stress.** See Of Interest To All, October 1-2.

October 28-29—**Psychological and Medical Management of Stress.** UCLA at Beverly Hilton Hotel, Beverly Hills. Friday-Saturday. 12 hrs.

November 14-18—**Group Therapy Seminars.** UCSF at Merri Hotel, Oakland. Monday-Friday.

RADIOLOGY AND PATHOLOGY

eptember 14—**Diagnostic Radiology.** LLU. 4 hrs. $25.

eptember 17—**Radiology Symposium—5th Annual.** Southern Calif. Permanente Medical Group at Bonaventure Hotel, Los Angeles. Saturday. Contact: Shirley Gach, So. Calif. Permanente Med. Grp., Education and Research Dept., 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

eptember 17—**Clinical Implications of New Diagnostic Techniques—Ultrasound, Cat Scan, Radioisotopes, Clinical Chemistry.** See Cancer, September 17.

ctober 4-7—**Recent Advances in Diagnostic Radiology.** UCSD. Tuesday-Friday.

ctober 8-16—**Body Imaging Conference—2nd Annual.** West Park Hospital, Canoga Park, at Kauai Surf Hotel, Kauai, Hawaii. One week. 25 hrs. $295. Contact: Ronald J. Freidman, MD, Dept. of Radiology, West Park Hospital, 22414 Roscoe Blvd., Canoga Park 91304.

ctober 21-23—**Society of Nuclear Medicine—2nd Annual Western Regional Meeting.** Aladdin Hotel, Las Vegas. Friday-Sunday. Contact: Justine J. Lynch, P.O. Box 40279, San Francisco 94140. (415) 647-0722 or (415) 647-5909.

ostgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 15 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY AND ANESTHESIOLOGY

ly 24-August 5—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200 for otolaryngologists; $900 for residents. Contact: Malcolm D. Graham, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

August 6—**Intensive Care—Fifth Saturday Symposium.** See Of Interest To All, August 6.

August 6-13—**Ophthalmology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

August 13-14—**Clinical Relevance of Recent Advances in Anesthesia: The Critically Ill Child and Adult.** STAN. Saturday-Sunday. 14 hours. Contact: Janie Sydow, Dept. of Anesthesiology, Stanford Univ. School of Medicine, Stanford 94305. (415) 497-6238.

August 15-20—**Intensive Review of Orthopaedic Surgery.** J. Vernon Luck Research Society at Airport Park Hotel, Inglewood. Monday-Saturday. $400. Contact: Chadwick F. Smith, MD, 2400 S. Flower St., Los Angeles 90007.

August 20-21—**Recent Advances in Respiratory Therapy.** California Society of Anesthesiologists at Sahara Hotel, Lake Tahoe. Saturday-Sunday. Contact: CSA, 100 S. Ellsworth Ave., No. 806, San Mateo 94401. (415) 348-1407.

August 22-24—**The Knee in Sports.** American Academy of Orthopaedic Surgeons at Hilton Hotel, San Francisco. Monday-Wednesday. $150, members; $200, nonmembers. Contact: AAOS, 430 N. Michigan Ave., Chicago 60611. (312) 822-0970.

August 27-September 2—**Edward Tyler Symposium on the Practical Management of the Infertile Couple.** See Obstetrics and Gynecology, August 27-September 2.

September 9-10—**Trauma.** UCSF at Mary's Help Hospital, Daly City. Friday-Saturday.

September 9-10—**Vascular Surgery.** UCSF. Friday-Saturday.

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September 15-16—**Pediatric Urology.** UCD at Hyatt Lake Tahoe. Thursday-Friday. 10 hrs. $150.

September 16-17—**Ophthalmology Update III.** PMC at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. 13 hrs. $225.

September 16-18—**Advances in Obstetrical Anesthesia.** UCSF at Hyatt on Union Square, San Francisco. Friday-Sunday. 12½ hrs.

October 10-14—**Congress of Neurological Surgeons.** Hilton Hotel, San Francisco. Monday-Friday. 40 hrs. $75, members; $100, nonmembers. Contact: David L. Kelly, Jr., MD, Bowman Gray School of Medicine, Winston-Salem, NC 27103. (919) 727-4653.

October 12-16—**Pacific Coast Fertility Society—Annual Meeting.** See Obstetrics and Gynecology, October 12-16.

October 23-November 4—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200 for otolaryngologists; $900, residents. Contact: Malcolm D. Graham, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

October 28-29—**The Macula.** Retina Research Fund of St. Mary's Hospital and Medical Center at Hyatt on Union Square, San Francisco. Friday-Saturday. Contact: Claire Ohiyon, c/o Howard Schatz, MD, 3637 Sacramento St., San Francisco 94118. (415) 921-4860.

October 30-November 4—**American Society of Plastic and Reconstructive Surgeons—Annual Convention.** Hilton Hotel, San Francisco. Sunday-Friday. 33 hrs. Contact: Linda Campbell, ASPRS, 29 E. Madison St., Chicago 60602. (312) 641-0593.

November 12—**Current Concepts in Ophthalmic Plastic Surgery.** Jules Stein Eye Institute, Los Angeles. Saturday. Contact: Shelley E. Reid, Jules Stein Eye Institute, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

November 18-19—**Strabismus.** PMC. Friday-Saturday. 16 hrs.

November 19—**Flexible Bronchoscopy Workshop.** PMC. Saturday. 6 hrs. $300.

November 19-20—**American Society of Anesthesiologists—Regional Refresher Course.** Sahara Hotel, Lake Tahoe. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

December 2-4—**ENG Workshop.** PMC at Ilikai Hotel, Honolulu. Friday-Saturday. 24 hrs. $395.

December 3—**Emergency Anesthesia.** Sacramento Valley Anesthesia Society; UCD; Calif. Society of Anesthesiologists at Red Lion Motor Inn, Sacramento. Saturday. $50. Contact: John H. Eisele, MD, Dept. of Anesthesiology. UCD Sch. of Med., Davis 95616. (916) 752-2703.

December 7-9—**Annual Ophthalmology Program.** UCSF. Wednesday-Friday.

December 14—**Treatment of Parkinsonism and Modern Concepts.** LLU. Wednesday. 4 hrs. $25.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

July 25-29—**Family Practice Refresher Course—4th Annual.** UCLA and Santa Monica Hospital at Century Plaza Hotel, Los Angeles. Monday-Friday. 40 hrs. $225.

July 31-August 5—**National Medical Association—82nd Annual Scientific Assembly.** Bonaventure Hotel, Los Angeles. Sunday-Friday. Contact: Alfred F. Fisher, Exec. Dir., NMA, 1625 Eye St., NW, Suite 725A, Washington, D.C. 20006.

August 6—**Intensive Care—Fifth Saturday Symposium.** Mercy Hospital and Medical Center, San Diego. Saturday. 8 hrs. Contact: Gilbert E. Kinyon, MD, Dir. of Anesthesia and Respiratory Therapy, Mercy Hosp. and Med. Ctr., 4077 Fifth Ave., San Diego 92103. (714) 294-8037.

August 8-9—**Autogenic Training and Biofeedback Workshop: Medical Approaches to Homeostatic Self-Regulation.** UCLA at Asilomar, Pacific Grove. Tuesday-Saturday. 24 hrs. $265.

August 13-24—**Postgraduate Refresher Course—20th Annual.** USC at Hawaii. 11 days. 37 hrs.

August 14—**Anatomy.** J Vernon Luck Research Society at Airport Park Hotel, Inglewood. Sunday. $125. Contact: Chadwick F. Smith, MD, 2400 S. Flower St., Los Angeles 90007.

August 15-19—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Islandia Hotel, San Diego. Sunday-Thursday.

August 22-27—**Family Practice Refresher Course—5th Annual.** UCD at Del Monte Hyatt House, Monterey. Monday-Saturday. 30 hrs. $225.

August 27-September 2—**Edward Tyler Symposium on the Practical Management of the Infertile Couple.** See Obstetrics and Gynecology, August 27-September 2.

August 29-September 3—**Family Practice Refresher Course—8th Annual.** UCI at South Coast Plaza Hotel, Costa Mesa. Monday-Saturday.

August 30-October 18—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland. Tuesday evenings.

September 11-15—**Emergency Medical Care Symposium.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Thursday. 37 hrs. $175.

September 19-23—**Topics in Emergency Medicine—Postgraduate Course for Career Emergency Physicians.** UCSF at Ralph K. Davies Medical Center, San Francisco. Monday-Friday. 40 hrs. $300.

September 24-25—**Drug Abuse (Psychopharmacology).** See Psychiatry, September 24-25.

September 24-25—**National Symposium on Patient Education.** UCSF; American Hosp. Assn.; National Bureau for Health Education; National Center for Health Education, Inc.; Society for Public Health Education, No. Calif. Chapter Stanford Univ. Hospital at UCSF. Saturday-Sunday. $65.

September 25-30—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Town and Country Hotel San Diego. Sunday-Friday.

October 1-2—**Nephrology for Family Physicians.** UCLA. Saturday-Sunday.

October 1-2—**Stress Management and Approaches to Stress.** UCSF at Sheraton Palace Hotel, San Francisco. Saturday-Sunday.

October 3-7—**Primary Care.** STAN. Monday-Friday.

October 6-8—**Western Occupational Health Conference—21st Annual.** Western Occupational Medical Assn. at Fairmont Hotel, San Francisco. Thursday-Saturday. Contact: B. F. Bravinder, Exec. Sec., WOMA, P.O. Box 201, Alamo 9450[illegible] (415) 837-0874.

October 6-9—**Clinical Pharmacology.** UCSF at Hilo, Hawaii. Thursday-Saturday.

October 7-8—**Neurology for the Non-Neurologist.** Mt. Zion Hospital and Medical Center, San Francisco. Friday-Saturday. Contact: Ann Raisbeck, Dept. of Med. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 9412[illegible] (415) 567-6600, ext. 2401.

October 8—**Selected Topics on Infectious Disease.** PMC. Saturday. 6 hrs.

October 12—**Pain and Its Management.** LLU. Wednesday. 4 hrs. $25.

October 12-14—**Alcoholism Course for Primary Care Physicians.** UCSD at Town and Country Hotel, San Diego. Wednesday-Friday.

October 12-16—**Pacific Coast Fertility Society.** See Obstetrics and Gynecology, October 12-16.

October 14-16, 21-23—**Introduction to Sex Counseling Principles.** UCSF Human Sexuality Program at UCSF. Two weekends. 50 hrs. $175, per person; $300, per couple. Contact: Susan Hansen, Human Sexuality Program, 350 Parnassus, Suite 700, San Francisco 94143. (415) 666-4787.

October 17-21—**Family Practice Review—2nd Annual.** LLU. Monday-Friday. 30 hrs. $150.

October 20-21—**Geriatrics.** UCSF at Veteran's Home of California, Yountville. Thursday-Friday.

October 24-28—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday.

October 28-29—**Psychological and Medical Management of Stress.** See Psychiatry, October 28-29.

October 30-November 3—**American Medical Association—Regional Meeting.** Sheraton Waikiki, Honolulu, Hawaii. Sunday-Thursday. Contact: AMA, 535 N. Dearborn, Chicago 60610.

October 31-November 4—**Intensive Care.** STAN. Monday-Friday.

November 6-9—**California Academy of Family Physicians—Annual Scientific Assembly.** Masonic Auditorium, San Francisco. Sunday-Wednesday. Contact: CAFP, 9 First St., San Francisco 94105. (415) 982-6091.

November 10-11—**Emergency Medicine (Advanced Course).** UCSF. Thursday-Friday.

November 12-13—**Rheumatology for Family Physicians.** UCLA. Saturday-Sunday.

December 12-16—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Islandia Hotel, San Diego. Monday-Friday.

December 14—**Treatment of Parkinsonism.** See Surgery, December 14.

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PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Physician-in-Residence Preceptorship in Pulmonary Disease. USC, Pulmonary Disease Section, Dept. of Medicine and Postgraduate Medical Education. One month or more, by arrangement. Opportunity for practicing physician to achieve specified knowledge and skills in adult pulmonary medicine. Contact: Oscar J. Balchum, MD, PhD, USC.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Department of Internal Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen R. Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, 97201.

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Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:
Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210.

University of Oregon Medical School, Infectious Disease Conferences, 3181 SW Sam Jackson Park Road, Portland.
Every Thursday, 12:00 Noon—**Infectious Disease Conference** (through June 2), Room 8B-60 UHS (University Hospital South).

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

INTERNAL MEDICINE

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

August 19-20—**Tomlin Memorial Cancer Lectures.** Rogue Valley Country Club, Medford. Contact: Earl L. Lawson, MD, The Medford Radiological Group, PO Box 1747, Medford 97501.

WASHINGTON, ALASKA, MONTANA AND IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-64, Seattle, Washington 98195. Phone: (206) 543-6995.

June 23-25—**Montana Academy of Family Physicians Annual Meeting.** Thursday-Saturday. Fairmont Hot Springs, Mont. Contact: R. D. Buchanan, MD, PO Box 220, Columbia Falls, MT 59912. (406) 892-3952.

July 27-30—**Idaho Medical Association Annual Meeting.** Wednesday-Saturday. Sun Valley, Idaho. Contact: Mr. Donald W. Sower, Exec. Dir., Idaho Medical Association, 407 W. Bannock St., Boise, ID 83701. (208) 344-7888.

August 29-September 2—**American College of Physicians MKSAP Course.** Monday-Friday. Health Sciences Auditorium, Univ. of Wash., Seattle. 36 hrs. Members, $140; ACP Associates, $70; non-member physicians, $200; residents, research fellows, $140. Contact: American College of Physicians, 4200 Pine St., Philadelphia, PA 19104. (215) 243-1200 or Division of Cont. Med. Ed., SC-64, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495.

September 22-25—**Washington State Medical Association Annual Meeting.** Friday-Sunday. Washington Plaza Hotel, Seattle. Contact: Mr. Harlan Knudson, Exec. Dir., Washington State Medical Association, 900 United Airlines Bldg., Seattle, WA 98121. (206) 623-4801.

September 29-October 1—**Montana Medical Association Annual Meeting.** Monday-Thursday. Village Motor Inn, Missoula, Mont. Contact: Mr. G. Brian Zins, Exec. Dir., Montana Medical Association, 2021 Eleventh Ave., Helena, MT 59601. (406) 443-4000.

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dications: Acute, recurrent or chronic urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli, Klebsiella-Aerobacter,* aphylococcus, *Proteus mirabilis* and, less frequently, *oteus vulgaris*), in the absence of obstructive uropathy or reign bodies. Note: Carefully coordinate *in vitro* sulnamide sensitivity tests with bacteriologic and clinical sponse; add aminobenzoic acid to follow-up culture edia. The increasing frequency of resistant organisms nits the usefulness of antibacterials including sulnamides, especially in chronic or recurrent urinary tract fections. Measure sulfonamide blood levels as variations ay occur; 20 mg/100 ml should be maximum total level.

ontraindications: Sulfonamide hypersensitivity; pregncy at term and during nursing period; infants less than o months of age.

arnings: Safety during pregnancy has not been estabhed. Sulfonamides should not be used for group A ta-hemolytic streptococcal infections and will not eradicte or prevent sequelae (rheumatic fever, glomerulonecritis) of such infections. Deaths from hypersensitivity reacns, agranulocytosis, aplastic anemia and other blood scrasias have been reported and early clinical signs ore throat, fever, pallor, purpura or jaundice) may indicte serious blood disorders. Frequent CBC and urinalysis h microscopic examination are recommended during sfonamide therapy. Insufficient data on children under s with chronic renal disease.

ecautions: Use cautiously in patients with impaired renal hepatic function, severe allergy, bronchial asthma; in glucse-6-phosphate dehydrogenase-deficient individuals in om dose-related hemolysis may occur. Maintain adeqate fluid intake to prevent crystalluria and stone formation.

verse Reactions: *Blood dyscrasias* (agranulocytosis, astic anemia, thrombocytopenia, leukopenia, hemolytic emia, purpura, hypoprothrombinemia and methemobinemia); *allergic reactions* (erythema multiforme, skin ptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimethamine in congenital toxoplasmosis). *Usual adult dosage:* 2 Gm (2 DS tabs or 4 tabs or 4 teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection.

Usual child's dosage: 0.5 Gm (1 tab or teasp.)/20 lbs of body weight initially, then 0.25 Gm/20 lbs *b.i.d.* Maximum dose should not exceed 75 mg/kg/24 hrs.

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Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

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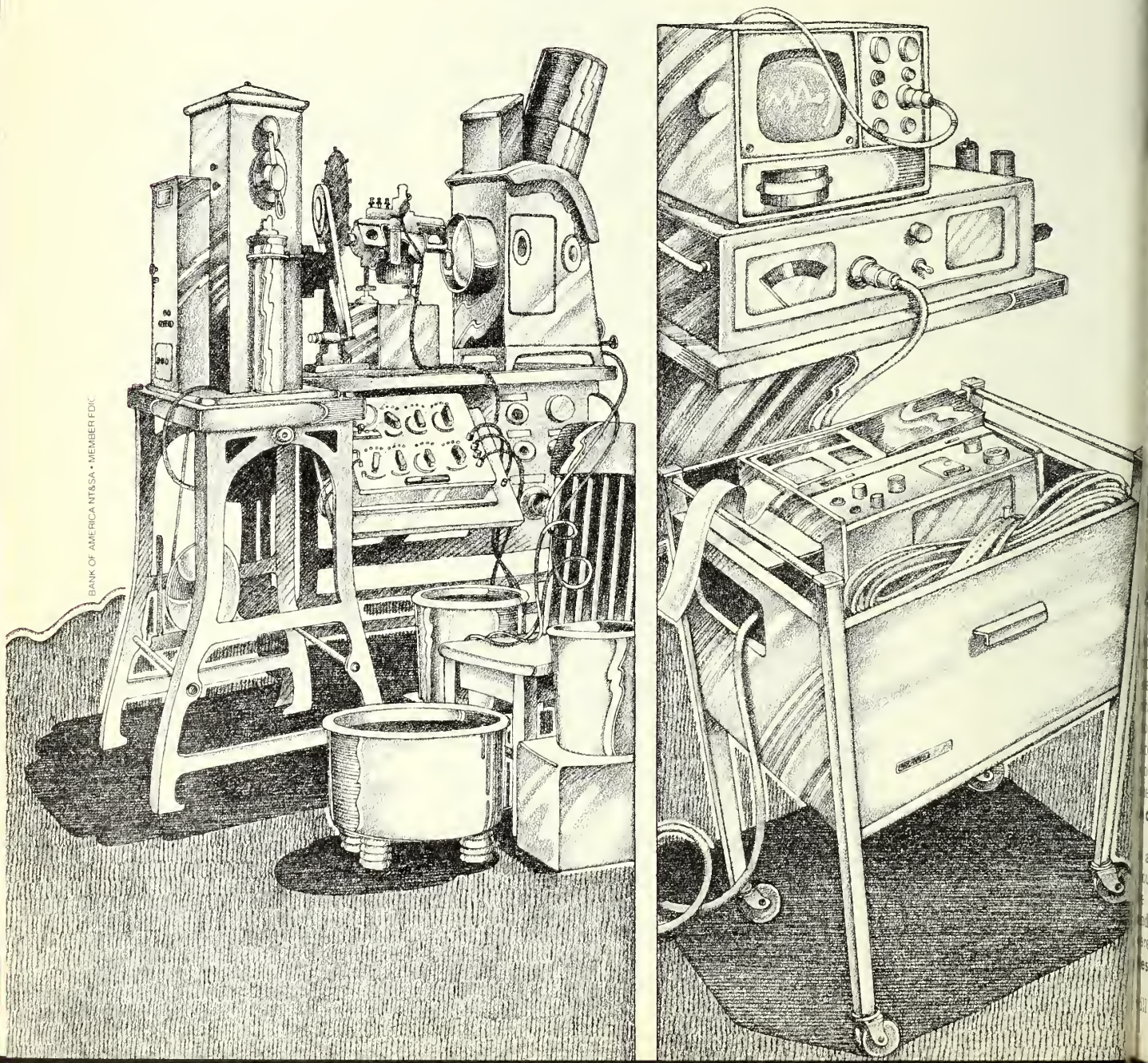

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Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

CURRENT OBSTETRIC & GYNECOLOGIC DIAGNOSIS & TREATMENT—1976—Ralph C. Benson, MD, Clinical Professor of Obstetrics & Gynecology and Emeritus Chairman, Department of Obstetrics & Gynecology, University of Oregon Health Sciences Center, Portland; and Associate Authors. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1976. 912 pages, $16.00.

DOWN'S ANOMALY—Second Edition—G.F. Smith, MD, Director of Genetics, Otago Medical School, Dunedin, New Zealand; and J.M. Berg, MB, BCh, MSc, MRC Psych, Professor of Psychiatry and Associate Professor of Medical Genetics, University of Toronto; Director of Genetic Services, Surrey Place Centre, Toronto. Churchill Livingstone - Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 348 pages, $26.50.

PSYCHOLOGICAL MEDICINE—An Introduction to Psychiatry—Eighth Edition—Desmond Curran, CBE, MB, FRCP, DPM, Lord Chancellor's Medical Visitor; Formerly Honorary Consulting Psychiatrist to St George's Hospital, Professor of Psychiatry, St. George's Hospital Medical School, University of London and Civil Consultant in Psychological Medicine to the Royal Navy; Maurice Partridge, DM, FRCP, DPM, Formerly Consultant Psychiatrist to St. George's Hospital and to the Royal Marsden Hospital, Lecturer and Vice-Dean, St. George's Hospital Medical School; and Peter Storey, MD, FRCP, FRCPsych, DPM, Consultant Psychiatrist to St. George's Hospital and Springfield Hospital, London. Churchill Livingstone - Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 444 pages, $14.50.

RECENT ADVANCES IN RESPIRATORY MEDICINE—Number One—Edited by T. B. Stretton, MB, FRCP, Consultant Physician, Manchester Royal Infirmary; Senior Lecturer in Medicine, University of Manchester. Churchill Livingstone - Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 311 pages, $32.50.

THE REMINISCENCES OF DOCTOR JOHN SEBASTIAN HELMCKEN—Edited by Dorothy Blakey Smith with an introduction by W. Kaye Lamb. University of British Columbia Press, 2075 Wesbrook Mall, Vancouver, BC, Canada (V6T1W5), 1975. 396 pages, $18.95.

SHOULD TREATMENT BE TERMINATED?—Thomas C. Oden, Professor of Theology and Ethics, Drew University, Madison, NJ Harper & Row, Publishers, Inc., 10 East 53rd St., New York City (10022), 1976. 93 pages, $2.95 (paperback).

SKIN SURGERY—Fourth Edition—Edited by Ervin Epstein, MD, Associate Clinical Professor of Dermatology, University of California, San Francisco: Chief of Dermatology and Syphilology at Highland-Alameda County Hospital, Oakland; Consultant to Oakland Area Veterans' Hospital; and Ervin Epstein, Jr., MD, Assistant Clinical Professor of Dermatology, Assistant Research Dermatologist, University of California, San Francisco: Consultant to Oakland Area Veterans' Hospital. Charles C Thomas, Publisher, 301-327 East Lawrence Ave., Springfield, IL (62717), 1976. 839 pages, $98.75.

SOCIAL RESPONSIBILITY: Journalism, Law, Medicine—Volume II—Edited by Louis W. Hodges, Director, Society and the Professions, Washington and Lee University. Washington and Lee University, Lexington, Virginia (24450), 1976. 104 pages, $2.50 paperbound (postpaid from the publisher).

SYSTEMIC PATHOLOGY—Second Edition—Volume I: Cardiovascular and Respiratory Systems. Edited by W. St. C. Symmers, MD(Belfast), PhD(Birmingham), FRCP(London), MRCP(Edinburgh), FRCPA Professor of Histopathology, University of London at Charing Cross Hospital Medical School; Honorary Consultant Pathologist, Charing Cross Hospital, London. Churchill Livingstone - Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 484 pages, $45.00.

A TEXTBOOK OF EPILEPSY—Edited by John Laidlaw, FRCP(Edin), Senior Physician to Chalfont Centre for Epilepsy; Physician in charge of the National Hospitals—Chalfont Centre for Epilepsy and Honorary Consultant to the National Hospital; and Alan Richens, PhD, MRCP, Senior Lecturer in Clinical Pharmacology, St. Bartholomew's Hospital, London; Honorary Consultant, The National Hospitals—Chalfont Centre for Epilepsy and Honorary Lecturer, Institute of Neurology, The National Hospital, London. Churchill Livingstone - Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 389 pages, $39.50.

TEXTBOOK OF PHYSIOLOGY AND BIOCHEMISTRY—Ninth Edition—George H. Bell, BSc, MD(Glasg), FRSE, Professor of Physiology in the University of Dundee: Honorary Fellow of the Accadèmia Anatomico-Chirurgica of Perugia; Donald Emslie-Smith, MD(Aberd), FRCP, FRCP-(Edin), Reader in Medicine in the University of Dundee; Honorary Consultant Physician, the Royal Infirmary and Ninewells Hospital, Dundee; and Colin R. Paterson, DM, BSc(Oxon), MRCPath, Senior Lecturer in Biochemical Medicine in the University of Dundee; Honorary Consultant to the Tayside Area Health Board. Churchill Livingstone - Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 733 pages, $20.00 (paperback).

VITAMIN C, THE COMMON COLD AND THE FLU—Linus Pauling. W. H. Freeman and Company, 660 Market Street, San Francisco (94104), 1976. 230 pages, $8.95 hardcover, $3.45 softcover.

(Continued on Page 14)

Brief Summary

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Alpha-hemolytic streptococci (viridans group)—Short-term prophylaxis of bacterial endocarditis prior to dental or other operative procedures in patients with a history of rheumatic fever or congenital heart disease who are hypersensitive to penicillin.

S. aureus—Acute infections of skin and soft tissue of mild to moderate severity. Resistant organisms may emerge during treatment.

S. pneumoniae (D. pneumoniae)—Upper and lower respiratory tract infections of mild to moderate degree.

M. pneumoniae — For respiratory infections due to this organism.

Hemophilus influenzae: For upper respiratory tract infections of mild to moderate severity when used concomitantly with adequate doses of sulfonamides. Not all strains of this organism are susceptible at the erythromycin concentrations ordinarily achieved (see appropriate sulfonamide labeling for prescribing information).

Treponema pallidum—As an alternate treatment in patients allergic to penicillin.

C. diphtheriae and C. minutissimum—As an adjunct to antitoxin. In the treatment of erythrasma.

Entamoeba histolytica—In the treatment of intestinal amebiasis.

L. monocytogenes—Infections due to this organism.

Establish susceptibility of pathogens to erythromycin, particularly when *S. aureus* is isolated.

Contraindications:

Known hypersensitivity to erythromycin.

Warnings:

Safety for use in pregnancy has not been established.

Precautions:

Exercise caution in administering to patients with impaired hepatic function. During prolonged or repeated therapy there is a possibility of overgrowth of non-susceptible bacteria or fungi. Surgical procedures should be performed when indicated.

Adverse Reactions:

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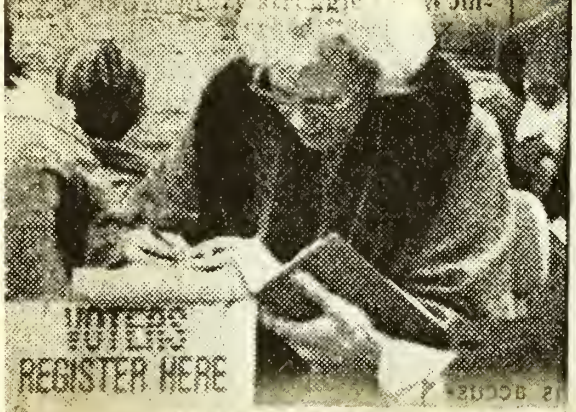
WASHINGTON, Aug. 26, 1920—



Social Security Bill Is Signed, Gives Pensions to Aged, Job

Roosevelt Approves Message Intended to Benefit 30,0 Persons When States Adopt Cooperating Laws—He the Measure 'Cornerstone' of His Economic Progr

WASHINGTON, Aug. 1 The Social Security Bill, a broad program of unem insurance and old age and counted upon to ben 20,000,000 persons, becan day when it was signed dent Roosevelt in the pr those chiefly responsible ting it through Co

Mr. Roosevelt cal "the cornerstone which is being me s comple rin to

SENATE APPROVES 18-YEAR OLD VOTE IN ALL ELECTIONS

Amendment to Constitution is Sent to House, Where Passage is Expected

WASHINGTON, March 10, 1971—The Senate approved today 94 to 0 and sent to

TRUMAN CLOSES ITED NATIONS CONFEREN WITH PLEA TO TRANSLATE CHARTER INTO DEEDS

NEW WORLD HOPE

President Hails 'Great Instrument of Peace,' Insists It Be Used

HISTORIC LANDMARK

Meeting Gives Standing Ovation as Executive Pictures Peace Gain

"If we fail to use it," he declared to the solemn final meeting of the delegates, 'we shall betray all of those who have died in order that we might meet here in freedom and safety to create it.'

"If we seek to use it selfishly—for the advantage of any one nation or any small group of nations—we shall be equally guilty of that betrayal."

Fervent Interpolation

The President, speaking in the auditorium of the War Memorial Opera House, built in memory of sons of the Golden Gate city who gave their lives in the first World War, in which he himself served, seemed to give unconscious expression to the solemn feeling of the occasion when, at the outset of his speech, he interpolated the words, half a hope, half a prayer:

"Oh, what a great day this can be in history!"

Just before the plenary session the President accompanied the

SIGN the Dra Ends N

WASHINGTON, Jan. 27, 1973—"With the signing of the peace agreement in Paris today, and after receiving a report from the Secretary of the Army that

PATIENT PACKAGE INSERTS: A CONCEPT WHOSE TIME HAS COME?

The consumer's right to know is an irreversible and desirable trend of the Seventies. It extends, and properly, to a patient's right to know more about his or her prescription medications. One way, gaining favor, is through patient package inserts. Wisely-prepared and properly distributed when medically indicated, they could markedly improve patient knowledge and drug therapy—laudable goals by anyone's standards.

The PMA endorses these goals and will work with government, the health professions and consumers to achieve them.

The Advantages

The concept holds promise of benefits: better patient understanding of the product prescribed, better adherence to the treatment plan, and more awareness of possible side reactions.

Every doctor has had patients who fail to finish antibiotic regimens because they feel better. Some patients assume that if one tranquilizer or analgesic is good, two may be twice as good. Still others fail to report dizziness while on antihypertensive therapy —and so on.

Problems like these might arise less often if the patient received written information in addition to verbal instructions. Some studies suggest that patients are more receptive to such materials, and they more often understand the verbal instructions and follow them, when inserts are used.

The Disadvantages

There are also some potential problems. Obviously, the inserts must be clearly phrased, without extraneous or complex detail. How much information is enough? How can it be kept current? Should all patients receive the same information? Should inserts be included with all drugs? Should only potential problems be listed or are patients better off with a "fair balance" presentation that describes usefulness as well as drawbacks?

These and similar questions require answers, since model inserts have yet to be properly developed and tested. Despite the need for these studies, the FDA is proceeding prematurely with inserts on selected products. We think the Congress is the only place where the matter can be given the proper legal status and direction, particularly since it represents a conceptual change in the legal, medical and social framework of the nation's prescription drug information system.

The Solution

The PMA believes that carefully-devised pilot studies of various kinds of inserts are needed. They should be developed and implemented with full participation by doctors, pharmacists, consumers, communications experts and the drug industry. Such studies will provide reliable pathways to follow, so that inserts will be useful aids to medical practice.

And particularly we think that you should be closely involved in this debate and in these studies and decisions. Otherwise, people with less experience and qualifications may control the purposes, content and use of a tool with considerable promise for improved patient care. It could make a difference in your practice tomorrow, and more importantly, in the health of your patients.

PMA
THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION
1155 FIFTEENTH ST. N. W. WASHINGTON, D. C. 20005

Books Received

(Continued From Page 10)

TO YOUR HEALTH—The Pleasures, Problems, and Politics of Alcohol— Richard S. Shore, MD, Assistant Clinical Professor, Department of Psychiatry, University of California, San Francisco, and psychiatrist in private practice, San Francisco; and John M. Luce, MD, Senior Resident in Internal Medicine, University of Colorado Medical Center, Denver. The Seabury Press, 815 Second Ave., New York City (10017), 1976. 230 pages, $12.95.

WATSON-JONES FRACTURES AND JOINT INJURIES—Volumes I and II: Fifth Edition—Edited by J.N. Wilson, ChM, FRCS, Consultant Orthopaedic Surgeon, Royal National Orthopaedic Hospital, London, and the National Hospitals for Nervous Diseases, Queen Square and Maida Vale; Surgeon in Charge of the Accident Unit, Royal National Orthopaedic Hospital, Stanmore; Fellow of the British Orthopaedic Association and the Royal Society of Medicine. Churchill Livingstone - Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 1372 pages in 2 volumes, $95.00.

BASIC SURGERY—Edited by John A. McCredie, MB, BCh, BAO, MCH (Belf), FRCS(Eng. & Edin), FRCS(Can), FACS, Associate Professor of Surgery and Therapeutic Radiology, University of Western Ontario; Illustrated by Carol Donner, BFA, AMI, Member, Society of Illustrators. Macmillan Publishing Co., Inc., 866 Third Avenue, New York, NY (10022), 1977. 660 pages, $15.95.

BT BEHAVIOR THERAPY—Strategies for Solving Problems in Living— Spencer A. Rathus, PhD, and Jeffrey S. Nevid, PhD. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1977. 314 pages, $8.95.

CHILD HEALTH IN THE COMMUNITY—A Handbook of Social and Community Paediatrics—Edited by Ross G. Mitchell, MD(Edin), FRCP(Edin), DCH, James Mackenzie Professor of Child Health, University of Dundee. Longman Inc., Churchill Livingstone - Medical Division, 19 West 44th Street, New York, NY (10036), 1977. 313 pages, $18.00.

CURRENT THERAPY 1977—Latest Approved Methods of Treatment for the Practicing Physician—Edited by Howard F. Conn, MD. W.B. Saunders Company, West Washington Square, Philadelphia (19105), 1977. 986 pages, $24.50

DIAGNOSTIC BRONCHOSCOPY—An Introduction: Third Edition—Peter Stradling, MD(Lond), FRCP, FRPS, Director of the Chest Clinic and Senior Lecturer in Respiratory Diseases, Royal Postgraduate Medical School, Hammersmith Hospital, London. Longman Inc., 19 West 44th Street, New York City (10036), 1976. 150 pages, $35.00

DIAGNOSTIC PATHWAYS IN CLINICAL MEDICINE—B. J. Essex, MB, MSc, MRCP, Late Senior Lecturer in Community Health Medical Faculty, University of Dar es Salaam, Tanzania; Foreword by W. J. Makane, Dean, Medical Faculty, University of Dar es Salaam. Longman Inc., 19 West 44th Street, New York City (10036), 1976. 173 pages, $9.95 (softbound).

ELEMENTS OF PSYCHOTHERAPY—Allen J. Enelow, MD, Professor of Health Behavior, University of the Pacific, Pacific Medical Center, San Francisco; Director, Division of Health Behavior, West Coast Cancer Foundation. Oxford University Press, 200 Madison Ave., New York City (10016), 1977. 146 pages, $8.95 (cloth), $3.95 (paper).

ENDOMETRIAL CARCINOMA AND ITS TREATMENT: The Role of Irradiation, Extent of Surgery, and Approach to Chemotherapy—Edited by Laman A. Gray, Sr., MD, Clinical Professor of Obstetrics and Gynecology, University of Louisville and University of Kentucky; Chairman, Professional Education Committee, American Cancer Society, Kentucky Division, Louisville. Charles C Thomas, Publisher. 301-327 East Lawrence Avenue, Springfield, IL (62717), 1977. 225 pages, $22.50.

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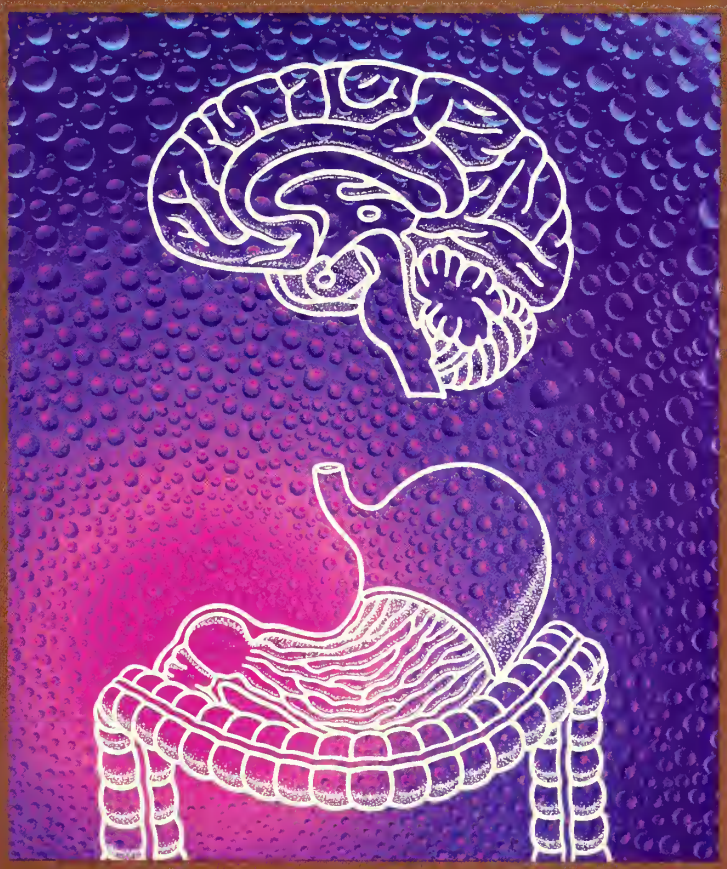

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THE WESTERN
Journal of Medicine

Refer to: Geschke W, Beutler E: Refractory sideroblastic and nonsideroblastic anemia—A review of 27 cases. West J Med 127:85-92, Aug 1977

Refractory Sideroblastic and Nonsideroblastic Anemia

A REVIEW OF 27 CASES

WILFRED GESCHKE, MD, *Portland, Oregon,* and ERNEST BEUTLER, MD, *Duarte, California*

A study was done with 27 patients who met the following criteria: (1) anemia, (2) cellular bone marrow not diagnostic of leukemia, (3) absence of underlying disease that could account for the hematologic abnormalities at time of initial study and (4) absence of iron, B_{12} or folate deficiency.

Of the 27 patients, 13 had ringed sideroblasts and 14 did not. Eleven patients received corticosteroids, 18 received folate, 23 pyridoxine and 12 androgens. Two partial responses occurred in the sideroblastic group and were attributed to androgen therapy in one patient and pyridoxine therapy in the other. In the nonsideroblastic group, two partial responses occurred which were attributed to prednisone therapy. Transfusions were required in 23 patients. Leukemia developed in six patients.

It is concluded that currently used treatments have little effect on refractory anemia and that in most patients continuing transfusions are required. In a small percentage of patients, there is transformation to leukemia.

REFRACTORY ANEMIA with normoplastic or hyperplastic marrow is a primary bone marrow disorder of unknown cause. It is generally unresponsive to specific forms of therapy such as administration of folic acid, vitamin B_{12} or iron, and at best is only partially responsive to treatment with androgens, pyridoxine and corticosteroids. It is often associated with leukopenia or thrombocytopenia, or both. This type of anemia has been variously referred to by designations such as primary refractory anemia, refractory normoblastic anemia,[1] refractory sideroblastic anemia,[2] pancytopenia with cellular marrow, chronic bone marrow failure,[3] refractory anemia with hyperplastic bone marrow and aregenerative anemia.[4] It should be distinguished from true aplastic anemia, in which the early stage may be associated with islands of active hematopoiesis, and from the congenital dyserythropoietic anemias which are characterized by erythroid multinuclearity and which may have associated cytopenias.[5]

Refractory anemia may be subdivided into two general categories: nonsideroblastic and sideroblastic. The purpose of this paper is to review the natural history of 27 cases of refractory sideroblastic and nonsideroblastic anemia.

Patients and Methods

All patients with anemia of at least a year's duration who were seen at the City of Hope Medical Center between 1958 and 1975 were

From the Department of Hematology, Division of Medicine, City of Hope National Medical Center, Duarte, California. Dr. Geschke is now in practice in Portland, Oregon.

Submitted October 13, 1976.

Reprint requests to: Ernest Beutler, MD, Division of Medicine, City of Hope Medical Center, 1500 E. Duarte Road, Duarte, CA 91010.

considered for inclusion in this study. Those patients in whom there were bone marrow findings diagnostic of leukemia or bone marrow aplasia when first seen, in whom systemic disease was found which might account for the anemia or in whom a deficiency was present in iron, vitamin B_{12} or folic acid were excluded.

First, histories were taken and physical examinations carried out in all patients who met the criteria enumerated above. With few exceptions the following studies also were done in all cases: x-ray studies of the chest, renal function studies, electrocardiograms and determinations of serum iron and iron binding capacity, blood glucose and uric acid. Hematologic studies included hemoglobin, red cell count, hematocrit, leukocyte count and differential, and platelet and reticulocyte counts. A minimum of two bone marrow examinations were done in all cases. Bone marrow specimens were obtained by aspiration from the sternum or iliac crest. Films were stained with Wright-Giemsa stain. To evaluate iron stores the Prussian blue reaction was used on both smears and sectioned aspirates. Sections were also stained with hematoxylin and eosin. Chromosome analysis of marrow cells or peripheral blood, or both, was done in nine patients.

Results

A total of 27 patients fulfilled the criteria for inclusion in the study. Each patient was classified as either sideroblastic or nonsideroblastic; 13 of the 27 patients had ringed sideroblasts and 14 did not. In the sideroblastic group there were 8 white males, 1 black male and 4 white females. At time of diagnosis the age range was from 6 to 79 years, with a median age of 62 years and a mean age of 60 years. In the nonsideroblastic group there were 9 white females and 5 white males. At time of diagnosis the age range was from 29 to 84 years, the median age 52 years and the mean age 54 years. The results of some of the physical findings and laboratory results are summarized in Table 1.

Physical Findings

Patients in both groups presented with the usual signs and symptoms of anemia. In the group of 13 patients with sideroblastic anemia, the liver was palpable in eight, extending from 1 to 6 cm below the right costal margin, and in two of the 13 patients splenomegaly was present, with the spleen palpable 3 to 7 cm below the left costal margin. In the group of 14 patients with nonsideroblastic anemia, the liver was palpable in eight, extending from 1 to 11 cm below the right costal margin and in five of the 13 patients splenomegaly was present, with the spleen palpable 2 to 5 cm below the left costal margin.

Blood Counts and Laboratory Findings

When the 13 patients with sideroblastic anemia were first seen at the City of Hope Medical Center, hemoglobin levels ranged from 7.1 to 12.5 grams per 100 ml (after transfusion), leukocyte counts from 2,500 to 10,450 per cu mm and platelets from 162,000 to 900,000 per cu mm. The reticulocyte counts in 11 of the 13 patients were low or normal, and increased in two cases. Serum iron levels were measured in ten of the 13 patients and all were in the upper range of normal or elevated. Uric acid levels were elevated in four of the 12 for whom determinations were carried out.

When the 14 patients with nonsideroblastic anemia were first seen at the City of Hope Medical Center, hemoglobin levels ranged from 4.4 to 11.4 grams per 100 ml, leukocyte counts from 1,600 to 6,900 per cu mm and platelets from 9,500 to 500,000 per cu mm. Reticulocyte counts

TABLE 1.—*Comparison of Features of Sideroblastic and Nonsideroblastic Anemia**

		Sideroblastic	*Nonsideroblastic*
Spleen (palpable)		2/13 patients	5/14 patients
Liver (palpable)		8/13 patients	8/14 patients
Hemoglobin level	mean	8.9 grams per 100 ml	7.8 grams per 100 ml
	median	9.1 grams per 100 ml	7.5 grams per 100 ml
Reticulocyte count	mean values	1.13 percent	1.24 percent
Leukocyte count		5,281 per cu mm	4,510 per cu mm
Platelets		318,000 per cu mm	222,000 per cu mm
Serum iron		207 mg per 100 ml	168 mg per 100 ml
Serum iron-binding capacity		317 mg per 100 ml	336 mg per 100 ml
Uric Acid		6.6 mg per 100 ml	6.4 mg per 100 ml

*All measurements represent initial values when patients were first seen at City of Hope.

in 11 of the 14 patients were normal or low, and increased in three cases. Serum iron levels were measured in seven of the 14 patients, and all were in the middle to high normal range or elevated. Uric acid levels were elevated in three of the 12 patients for whom determinations were done.

Bone Marrow Findings

In the sideroblastic group, increased erythropoiesis was present in the marrow of 12 of the 13 patients. In 12 of the 13 patients increased iron stores were noted. Megakaryocytes were normal or increased in number and myelopoiesis was decreased, normal or increased.

On bone marrow examination in the nonsideroblastic group of 14 patients, varied erythroid, myeloid and megakaryocytic activity was found. Iron stores were increased in most of the cases but were normal or initially decreased in several patients.

Karyotypes

Bone marrow karotypes were done in four of the sideroblastic cases, with three yielding normal results. In the fourth patient (patient 6) there was an initially normal karyotype in 1965 but a later karyotype in 1966 had pseudodiploidy and evidence of chromatid breaks, monosomy for chromosome #20 and an abnormal metacentric chromosome.

In five patients in the nonsideroblastic group, bone marrow karyotypes were done. The result was normal in one case, but in the remaining four the following separately encountered abnormalities were present: pseudodiploidy, chromosome breaks, long-arm deletion and aneuploidy.

Treatment and Course

In the sideroblastic group, 3 patients were treated with corticosteroids, 9 with folate, 13 with pyridoxine and 5 with androgens. Four of the 13 patients treated with pyridoxine received it before coming to City of Hope. The remaining nine patients treated with pyridoxine received it in a range of 50 to 400 mg per day from 1.5 months to ten years, with the exception of 1 patient who received 200 mg per day for three weeks. Two patients received experimental treatment, one with cytosine arabinoside given intravenously (6 five-day courses of 1 to 2 mg per kg of body weight per day), and one with pyridoxal phosphate given intramuscularly (250 mg per day for ten days). Eleven of the 13 patients did not respond to treatment. In one patient (patient 11) there was a transient, modest rise in the hemoglobin level following androgen therapy, but this partial response was terminated by the development of Coombs positive hemolysis necessitating treatment with prednisone. Thereafter, infrequent transfusions have been required. In another patient (patient 3) there was a mild rise in the hemoglobin value following pyridoxine therapy. In patient 4 there was a brief reticulocytosis while pyridoxine was being given but no rise in the hemoglobin value. Twelve of 13 patients received multiagent therapy. Transfusions were required in nine patients.

Patients in the nonsideroblastic group were treated as follows: 8 received corticosteroids, 9 folate, 10 pyridoxine, 2 vitamin B_{12}, 2 cobaltous chloride, 7 androgens and 1 received only transfusion therapy. Four of the ten patients treated with pyridoxine received it before coming to City of Hope. The remaining six patients received pyridoxine in a range of 150 to 600 mg per day for from three months to two years. Two patients received cytoxan (range of 50 to 150 mg per day given by mouth for about 1 to 2 months), four patients received cytosine arabinoside intravenously (1 to 4 five-day courses of 1 to 2 mg per kg of body weight per day), one patient received thioguanine (100 mg by mouth every day for five days) and one patient received 6-mercaptopurine (25 mg by mouth every day for five days) as experimental therapy. In 12 of 14 patients no significant response to treatment was seen, although in 2 patients (patients 19 and 25) there was a brief reticulocytosis without a rise in hemoglobin values during pyridoxine therapy. Two patients entered partial remission. Prednisone was considered a possible cause of one partial remission (patient 14). Before prednisone was used, the patient was treated with androgens, vitamin B_{12}, folate, iron, pyridoxine, cobaltous chloride, Valentine's liver extract, adenine, cytosine and cytodylic acid without benefit.

The other patient (patient 21) entered partial remission while receiving long-term prednisone therapy two years after receiving cytosine arabinoside. Twelve of 14 patients received multiagent therapy. Transfusions were required in all patients in the nonsideroblastic group. Fewer than half the patients in the two combined groups were treated with iron or vitamin B_{12} (or both) before evaluation at the City of Hope Medical Center.

TABLE 2.—*Patients with Sideroblastic Anemia*

Patient, Race and Sex	Year Anemia Dx	Age at Dx	Hb gms per 100 ml / Retic. Count Percent	Leukocytes/ cu mm	Platelets ×1,000/ cu mm	Outcome	Serum (μg per 100 ml) Fe	Serum (μg per 100 ml) IBC	Initial Marrow (Sideroblastic)	Uric Acid	Transfusions	Karyotype	Liver Cm	Spleen Cm
1W♂ ...	1957	43	9.8 1.0	3,500	179	Stable without treatment	287	315	E↑MK→MY↓I↑	6.5	0	.....	0	0
2W♀ ...	1959	62	9.6 1.1	4,500	360	Stable without treatment	194	332	E↑MK→MY↓I↑	3.0	3	.....	1	0
3W♂ ...	1959	6	7.6 0.4	10,450	900	Stable without treatment	246	520	E↑MK↑MY→I→	3.8	5	Normal male 46 XY	3	Abst.
4W♂ ...	1963	58	9.3 5.4	4,000	205	No response to treatment	275	280	E↑MK→MY→I↑	7.2	0	Normal male 46 XY	2	3
5W♀ ...	1964	58	7.3 2.3	4,300	196	Stable without treatment	159	202	E↑MK↑MY→I↑	6.0	0	.....	2	0
6W♀ ...	1965	76	7.4 ..	4,400	217	No response to treatment	160	165	E↑MK→MY↑I↑	13.8	29	Normal female 1965 Abnormal 1966 (see text)	0 ↓ 6	0 ↓ 7
7W♂ ...	1966	54	7.4 0.1	6,800	510	Died 1970, acute leukemia	242	500	E↑MK↑MY→I↑	..	57	.....	6	0
8W♂ ...	1968	68	10.7 1.0	7,300	230	Died 1971, myocardial infarction	190	300	E↑MK→MY→I↑	9.7	44	.....	6	0
9W♀ ...	1969	78	12.5* 0*	4,900	225	Died 1971, myocardial infarction	..	..	E→MK↑MY↑I↑	3.9	?	.....	0	0
10W♂ ...	1970	79	10.9 0.3	6,300	322	Died 1974, congestive heart failure, arterio-sclerotic heart disease	..	..	E↑MK↑MY→I↑	4.2	52	.....	2 ↓ 6	0
11W♂ ...	1972	69	9.1 1.1	4,500	246	Continuing transfusion requirement	..	..	E↑MK↑MY→I↑	4.2	?	Normal male 46 XY	0	0
12B♂	1973	61	7.1 0.2	2,500	162	Continuing transfusion requirement	188	262	E↑MK↑MY→I↑	7.7 ↓ 8.6	27	.....	0	0
13W♂ ...	1974	68	7.9 0.6	5,200	380	No response to treatment	133	294	E↑MK→MY→I↑	8.4	0	.....	0	0

*Immediately after transfusion.

E = Erythropoiesis
Hb = Hemoglobin
MK = Megakarocytes
MY = Myelopoiesis
I = Iron
IBC = Iron-binding capacity
↑ = Increase
→ = Normal
↓ = Decrease
W = White
B = Black

TABLE 3.—*Patients with Nonsideroblastic Anemia*

Patient, Race and Sex	Year Anemia Dx	Age at Dx	Hb gms per 100 ml / Retic. Count Percent	Leukocytes/ cu mm	Platelets ×1,000/ cu mm	Outcome	Serum (μg per 100 ml) Fe	Serum (μg per 100 ml) IBC	Initial Marrow (Nonsideroblastic)	Uric Acid	Transfusions	Karyotype	Liver Cm	Spleen Cm
14W♀ ...	1956	29	5.8 1.4	4,550	86	Entered partial remission 1968	153	290	E↑MK↓MY→I→	3.9	26	.....	0	0
15W♀ ...	1957	51	4.4 0.4	3,850	500	Died 1975, congestive heart failure (hemochromatosis)	153	358	E↓MK↑MY→I↑	6.1	229	.....	2 ↓ 8	0 ↓ 5
16W♀ ...	1964	29	8.8 0.2	4,950	165	Died 1971, unrelated cause	..	..	E↓MK→MY↑I↑	..	7	.....	1	0
17W♀ ...	1965	41	11.4 0.6	6,900	176	Died 1975, acute leukemia	140	318	E→MK↑MY→I→	3.9	?	Deleted long arm of chromosome #5	8	3
18W♀ ...	1970	84	11.3 0.5	4,100	70	Died 1972, acute leukemia	..	..	E↑MK↑MY→I→	..	71	.....	6	0
19W♂ ...	1970	48	9.2 0.6	4,100	340	Died 1975, acute leukemia	106	235	E↑MK↑MY↑I↓↑	5.3	50	46 XY Pseudodiploidy	2 ↓ 5	2 ↓ 4
20W♀ ...	1970	65	8.6 4.2	6,400	380	Died 1975, ? cause	6	0	E→MK↑MY↑I↑	9.6	?	.....	0	0
21W♂ ...	1971	34	6.9 0.4	1,600	9.5	Entered partial remission 1975	255	678	E↑MK↓MY↓I↓↑	4.5	115	.....	0	0
22W♂ ...	1971	62	6.8 0.5	6,100	275	Transformation to chronic myelomonocytic leukemia, died 1976	..	..	E↓MK→MY↑I?	4.6	135	.....	11	5
23W♀ ...	1971	58	7.1 0.2	3,400	120	Died 1974, unrelated cause	..	..	E↓MK↓MY→I↑	4.4	96	.....	0 ↓ 5	2
24W♀ ...	1973	70	7.8 0.2	4,100	300	Died 1975, unrelated cause	177	228	E↑MK→MY↓I↑	10.0	59	No specific chromosome abnormalities	3	0
25W♂ ...	1973	51	5.4 3.5	5,200	415	Transfusion requirements continue	191	244	E↑MK→MY→I↑	14.2	45	2 out of 22 cells had breaks in one of the chroms (9%)	0	0
26W♀ ...	1974	54	7.2 4.4	5,500	124	Transfusion requirements continue	..	..	E↑MK→MY↑I↑	4.8	6	14% aneuploidy	0	0
27W♂ ...	1974	79	7.8 0.3	2,400	152	Died acute leukemia 1975	..	..	E↓MK↓MY↑I↑	5.8	8	.....	0	0

E = Erythropoiesis
Hb = Hemoglobin
MK = Megakarocytes
MY = Myelopoiesis
I = Iron
IBC = Iron-binding capacity
↑ = Increase
→ = Normal
↓ = Decrease
W = White

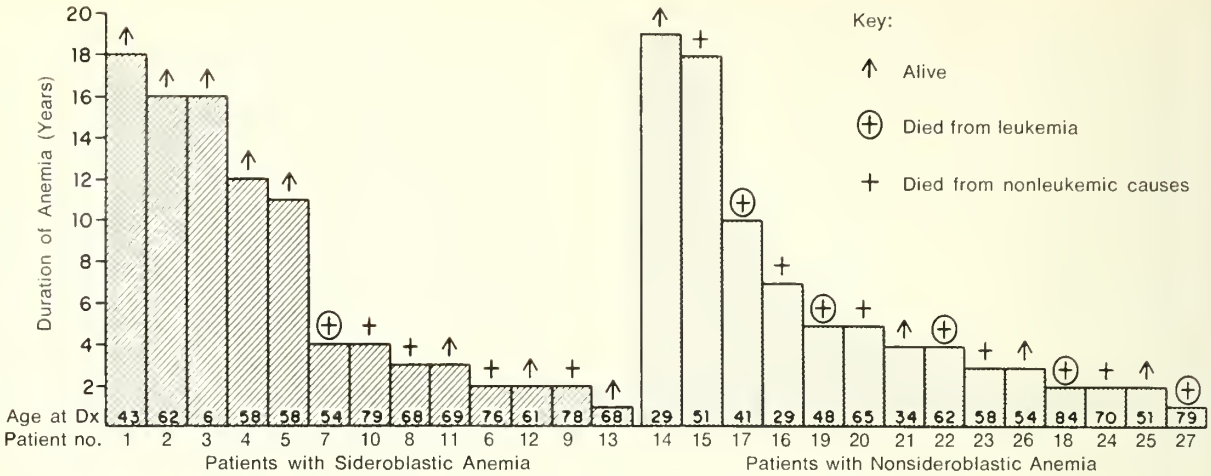

Figure 1.—Duration of anemia and outcome of 27 cases of refractory anemia.

The clinical course of each patient is summarized in Tables 2 and 3. Figure 1 shows a comparison of the duration of anemia in the 27 patients. In the nonsideroblastic group acute leukemia developed in four patients, in one of whom (patient 17) anemia had been present for ten years. In one patient (patient 22) in the nonsideroblastic group chronic myelomonocytic leukemia developed. In only one patient in the sideroblastic group did acute leukemia develop. However, two patients with sideroblastic refractory anemia were not entered into the study because acute leukemia had developed in each within less than a year after anemia developed; therefore they did not fulfill the criteria used in selecting patients for this survey.

Discussion

The major feature that distinguishes primary acquired refractory anemia from aplastic anemia is the degree of bone marrow cellularity; in the former the marrow ranges from normocellular to intensely hypercellular, whereas in the latter the marrow is almost devoid of hematopoietic tissue. Patients with primary acquired refractory anemia may be classified as having either refractory sideroblastic anemia or refractory nonsideroblastic anemia. Studies of the bone marrows of patients with sideroblastic anemia show the presence of numerous normoblasts containing large amounts of stainable iron arranged in a ring surrounding the nucleus. These cells, the so-called "ringed sideroblasts," contain mitochondria which are distended with nonferritin iron; in contrast, normoblasts from normal subjects contain iron primarily in the form of cytoplasmic ferritin aggregates.[9]

An important feature common to both sideroblastic and nonsideroblastic anemia is ineffective erythropoiesis. Dacie and co-workers studied seven cases of sideroblastic anemia and showed there to be poor utilization of intravenously administered radioactive iron (^{59}Fe): there was subnormal delivery of tagged red cells into the peripheral blood in conjunction with a rapid turnover of iron in the plasma.[1] Sultan reported that the bone marrows of six patients with refractory anemia were incapable of forming colonies *in vitro* on agar gel medium and in that respect acted as do bone marrows from patients with acute myelogenous leukemia in relapse.[6]

Leukopenia or thrombocytopenia (or both) may coexist with the anemia. White cell abnormalities that have been reported include: Pelger-Huêt granulocytes, granulation defects in polymorphonuclear leukocytes, occasional immature granulocytes, monocytosis, atypical monocytes and bizarre platelets.[7] Platelet adhesiveness and aggregation abnormalities have been reported in cases of sideroblastic anemia.[8]

Observations on 35 patients with primary sideroblastic anemia were published by MacGibbon and Mollin.[10] Three of the patients were boys with hereditary sex-linked anemia. However, most of the patients were elderly, with an average age of 70 years; 60 percent were female. Characteristic hematological features included low reticulocyte percentage, pronounced erythroid hyperplasia, often megaloblastic, serum iron and percentage saturation of total iron-binding capacity frequently raised, and an insignificant decrease or no decrease in mean red cell lifespan. Pyri-

doxine therapy (1 to 100 mg per day) was used in 27 patients. In 37 percent there was hematologic response, frequently only partial but occasionally almost complete (a hemoglobin level at least 14 grams per 100 ml, but with hypochromic red blood cells and persistence of ring sideroblasts).

Our observations are similar with regard to reticulocyte percentage, degree of erythroid hyperplasia of the marrow and serum iron studies. The response to therapy of our patients was strikingly different from that reported by MacGibbon and Mollin, however. In our group only two of 13 sideroblastic patients responded and only partially, one to androgens and the other to pyridoxine therapy.

A study of ten cases of refractory sideroblastic anemia was reported by Barry and Day.[11] Two patients had splenomegaly and 3 had hepatomegaly. The hemoglobin levels ranged from 5 to 10 grams per 100 ml. The initial leukocyte counts were low in five patients, the lowest level being 2,700 per cu mm. Platelet levels were low, normal or elevated. Folate treatment did not significantly change the basic features. Six patients received transfusion therapy. One patient with a history of exposure to benzol died of acute monoblastic leukemia 13 years after anemia was first discovered. In our group of 13 sideroblastic patients we found that a smaller percentage had splenomegaly and a larger percentage hepatomegaly. Hemoglobin values, white cell counts and platelet levels were similar in the two groups. Folate therapy was of no significant benefit in either group. In both series of sideroblastic patients there was one who died from acute leukemia. In most of the patients in both groups transfusion therapy was required.

Kushner and associates reported the results of clinical and laboratory investigations of 17 patients with idiopathic refractory sideroblastic anemia.[12] The age range was from 54 to 88 years. At the time of initial physical examination the liver was palpable in seven patients and the spleen was palpable in five patients. In the 17 patients the hematocrit reading ranged from 22 to 38 percent. Erythroid hyperplasia of the marrow and increased marrow iron were characteristic. Hyperferremia was present in 12 of the 17 patients at the time of initial study. In seven patients periodic transfusions were required. Nine patients received androgens alone or in combination with prednisone for a minimum of three months. In three of the nine patients there was significant improvement. Ten patients received pyridoxine (50 to 200 mg per day) and none responded. One patient died with acute myeloblastic leukemia seven years after the onset of sideroblastic anemia.

The age range of our patients was somewhat younger. Similarities include bone marrow patterns and serum iron levels. A higher percentage of patients in our group required periodic transfusions. Fewer of our patients responded to drug therapy but the infrequent response to pyridoxine in the series of Kushner and co-workers parallels our experience and stands in contrast to the high frequency of response reported by MacGibbon and Mollin.[10]

The heterogeneity of refractory anemia with hyperplastic bone marrow was emphasized by Vilter and associates, who separated patients into five types.[13]

It has been considered that the first stage of Di Guglielmo syndrome (erythremic myelosis) is frequently identical to sideroblastic anemia.[14] Di Guglielmo syndrome may exist in a chronic form beginning as a refractory anemia (preleukemia) and terminates years later as leukemia.[15] Block and associates listed primary refractory anemia with hyperplastic marrow among the differential diagnoses which may be considered in the preleukemic phase of acute leukemia.[16] Bauters and co-workers reported that out of a series of 15 cases of refractory anemia, the condition transformed to acute myeloblastic leukemia in five patients. Two of the 15 patients had sideroblastic anemia and were not among those in whom acute leukemia developed.[17]

In our series of 13 sideroblastic patients, acute leukemia developed in one, whereas in the 14 nonsideroblastic patients acute leukemia developed in four and chronic myelomonocytic leukemia in one (patient 22).

Chromosome abnormalities are known to occur in refractory anemia. In a series of six cases of acquired sideroblastic anemia, five patients were found to have abnormalities. In two cases a partial deletion of an arm of a chromosome 19-20 occurred and in three cases a rearrangement of a chromosome 19-20, which probably represented pericentric inversion was shown to have occurred.[18]

In our series of 27 cases of refractory anemia, chromosome analysis was done in nine patients.

In five the karyotype was normal; however, a later change to abnormal occurred in one patient (patient 6, sideroblastic).

We conclude that patients with refractory sideroblastic and nonsideroblastic anemia have a highly variable course with regard to duration of anemia (Table 3). In most cases transfusion requirements develop. Responses to forms of therapy such as androgens, pyridoxine, folate and corticosteroids occur infrequently and are partial, at best. In a small percentage of patients, transformation to acute leukemia occurs and this may happen even after many years.

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The Relationship Between Colorectal Polyps and Carcinoma

DR. TROLLOPE: "Yes, indeed, there is a relationship between polyps and carcinoma, and this seems true not only for the villous adenomas that we have agreed upon in the past, but also for even small adenomatous polyps. . . . Second, any patient with any size polyp shown on barium enema should be considered for colonoscopic polypectomy. Third, colon resection for polyps with carcinoma is indicated only in certain circumstances (when it is down in the base, when it is in the lymphatics, and so on). Finally, in every patient after polypectomy has been done a barium enema study and sigmoidoscopy should be carried out yearly until five consecutive examinations have given normal findings."

—MICHAEL L. TROLLOPE, MD, *Palo Alto, CA*

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Refer to: Sells CJ, Shurtleff DB: Cerebrospinal fluid shunts. West J Med 127:93-98, Aug 1977

Cerebrospinal Fluid Shunts

CLIFFORD J. SELLS, MD, *and* DAVID B. SHURTLEFF, MD, *Seattle*

Cerebrospinal fluid (CSF) shunt technology has undergone rapid advances in the past two decades. As a result, pediatricians and other primary care physicians are being asked with increasing frequency to provide care for persons with CSF shunts. Familiarity with the more common shunts is a prerequisite to intelligent management of shunt related problems. Physicians providing daily care must have carefully documented hospital records and operative notes available to them as well as information detailing the safe evaluation of shunt patency and function if they are to manage patients with CSF shunts properly. In addition, parents and guardians must be alerted to signs and symptoms related to shunt malfunction.

CEREBROSPINAL FLUID (CSF) shunting systems and shunt technology have undergone rapid advances over the past two decades.[1-9] Pediatricians and other primary care physicians are being asked with increasing frequency to care for children with CSF shunts. The differentiation of shunt complications from non-shunt related problems and the management of acute shunt obstruction and infection, particularly when neurosurgical colleagues are unavailable, requires pediatricians and other physicians to understand CSF shunt mechanisms.

Newly developed shunt systems include several externally similar but structurally and functionally different devices.*[2] Some devices can be safely punctured by a small gauge needle for aspiration for diagnosis, for the injection of antibiotics or radioisotopes and for pressure measurements; but other devices cannot. Some shunts have bidirectional flow and allow access to both the cerebral ventricle and the distal limb, while others provide unidirectional flow only and allow access only to a portion of the shunt mechanism. Familiarity with the more common shunts and an understanding of the potential of reservoirs, pumps and valves is a prerequisite to appropriate management of acute shunt obstruction and infection. The purpose of this article is to provide primary care physicians with basic technical information about cerebrospinal fluid shunting systems.

Types of Systems

Cerebrospinal fluid shunt systems may be divided into six groups depending upon their physically palpable parts. Reservoirs (Figure 1) are devices without internal parts with no shunting capabilities unless converted. They provide access to the cerebral ventricle for drug injection, aspiration or pressure recordings, but have no palpable distal tubing. They may have side-arm

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*Devices or elements are sometimes used as synonyms for valves, pumps, or reservoirs. In this article, device and element are used as general terms. The use of the word valve is restricted to describing a device or element with internal parts providmg one- or two-way flow.

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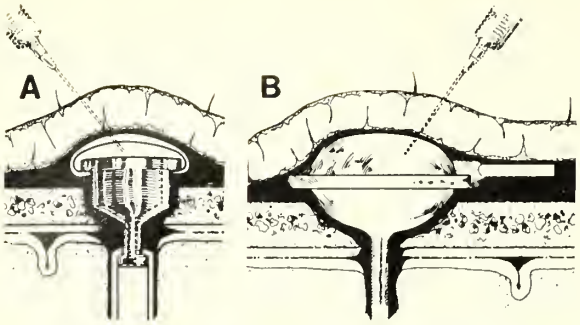

Figure 1.—Reservoirs. These elements have neither internal parts nor cerebrospinal fluid shunting capabilities unless converted and are safely perforable. **A,** Rickham Reservoir—Metal reservoir with soft cap without side-arm. **B,** Convertible Ommaya Reservoir—All soft parts reservoir with optional side-arm for later connection to a shunt system.

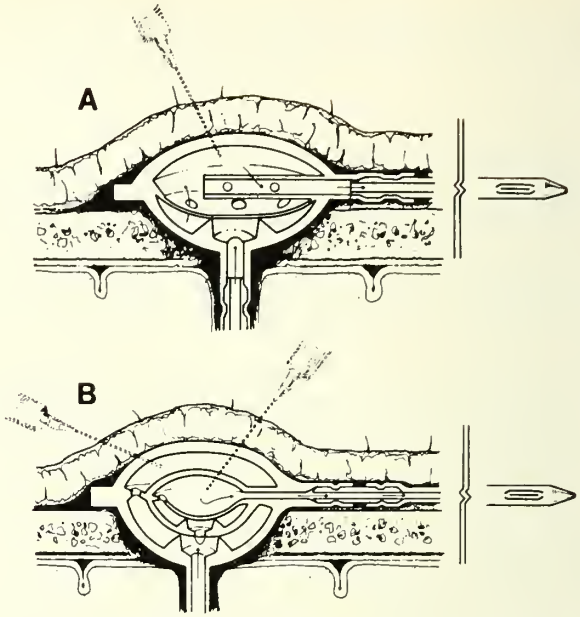

Figure 2.—Single Dome Devices with Palpable Distal Tube (Pictured with Pudenz One-Way Distal Slit Valve—the distal tip of either cardiac or peritoneal catheters). **A,** Pudenz One-Way Flushing Reservoir. **B,** Mishler Pudenz Double Lumen Reservoir. This unit combines an inner distal direction pumping device surrounded by an outer proximal direction pumping device. Both reservoirs are safely perforable.

attachments for later coupling to a distal device, thereby allowing for continuous CSF drainage.

A second group of systems consist of a single dome-shaped device and a single palpable distal tube leading to the neck (Figure 2). These devices, as are all Heyer systems, are used with Pudenz one-way distal slit valve catheters (Figures 2-6). The Pudenz One-Way Flushing Reservoir (Figure 2A) and the Mishler Pudenz Double Lumen Reservoir (Figure 2B) are two members of this group. The Pudenz One-Way Flushing Reservoir allows CSF aspiration from the proximal end and distal flushing either by injection or external dome pressure. Needle puncture of the inner, or lower chamber may result in valve incompetency. The Mishler Pudenz Double Lumen Reservoir has two chambers. The outer chamber permits aspiration from the cerebral ventricle only. Injection into the outer chamber or slight dome compression forces CSF simultaneously toward both proximal and distal shunt limbs, toward the cerebral ventricle with distal limb occlusion or obstruction* or toward the distal shunt limb with proximal limb obstruction. The inner chamber of the Mishler Pudenz Double Lumen Reservoir permits aspiration from both chambers as well as from the proximal limb and cerebral ventricle. Injection into the inner chamber or firm dome pressure will push CSF distally only. A firm or resistant outer chamber indicates distal and either inner chamber or proximal limb obstruction. A firm or resistant inner chamber indicates distal limb obstruction only. Failure of the outer chamber to refill after compression indicates proximal limb obstruction, while failure of the inner chamber to refill after compression indicates either outer to inner chamber or proximal limb obstruction. Intermittent external pressure (pumping) on the inner chamber of the Mishler Pudenz Double Lumen Reservoir or on the Pudenz One-Way Flushing Reservoir will result in distal CSF flow. The devices shown in Figures 1 and 2 lie over or partially in a cranial burr hole.

A third group of systems has a proximal tube leading from the cranial burr hole to a single dome element as well as a distal tube leading to the neck. These single dome devices may or may not have a one- or two-way valve with or without cerebral access. Members of this group may be difficult to differentiate clinically from each other. The Foltz To and Fro Flushing Reservoir (Figure 3A) and the Mishler Pudenz Double Lumen Reservoir with flat bottom (Figure 3B) are two examples of this group. The Foltz Reservoir with proximal tube occlusion or obstruction allows access to the distal limb during injection into or pressure on the dome, causing CSF to flow distally. With occlusion of the distal limb, injection into or pressure on the dome forces CSF

*Occlusion implies CSF blockage by external manual compression while obstruction implies intratubing blockage to CSF flow.

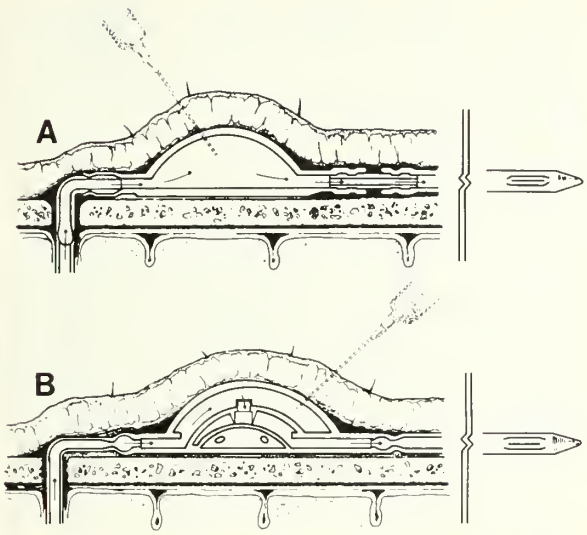

Figure 3.—Single Dome Devices with Two Palpable Shunt Tubes (Pictured with Pudenz One-Way Distal Slit Valve). **A,** Foltz To and Fro Flushing Reservoir. This device is safely perforable. **B,** Mishler Pudenz Double Lumen Reservoir with Flat Bottom. Both chambers are safely perforable.

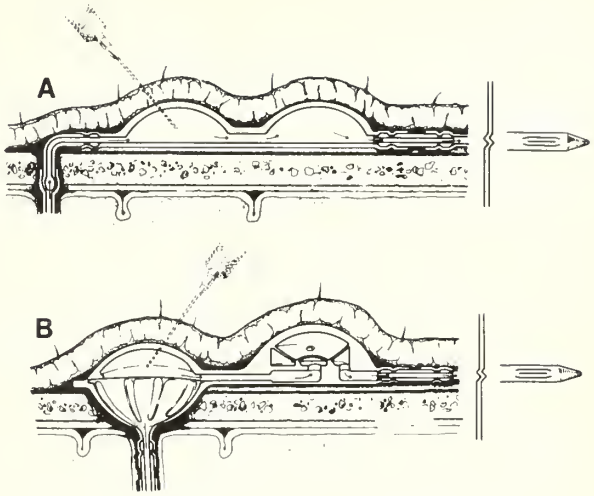

Figure 4.—Double Dome Systems (Pictured with Pudenz One-Way Distal Slit Valve). **A,** Braden Reservoir. This unit has two soft compressible domes mounted on a palpable oblong platform and functions similarly to the Foltz To and Fro Flushing Reservoir. By occluding the inlet/outlet domes access is gained to the distal or proximal end of the system. Both domes are safely perforable. **B,** Coe-Schulte Flushing Reservoir. This unit has a proximal soft and a distal firm compressible dome. Constant pressure on the distal dome occludes forward flow, allowing ventricular access with injection into or pressure on the proximal dome. Repetitive pressure on the distal dome pumps cerebrospinal fluid distally. Although cerebrospinal fluid may be aspirated from either dome, perforation of the inner distal device (dome) may cause damage.

flow proximally and may "blow out" a ventricular end obstruction. Repetitious finger pressure first on the proximal tubing and then simultaneously on the dome causes CSF to flow distally. A firm dome with occlusive pressure on either limb indicates obstruction in the other limb. A firm, noncompressible dome indicates distal and proximal tube occlusion. The Mishler Pudenz Double Lumen Reservoir with the flat bottom and the standard Mishler Pudenz Double Lumen Reservoir have similar palpable and functional characteristics except for the palpable proximal tube with the flat bottom device which can be occluded, therefore assuring CSF flow distally with dome compression. A fourth group of systems has two round dome elements, may or may not have valves and is capable of occlusion and pumping functions. The Braden Reservoir (Figure 4A) and the Coe-Schulte Flushing Reservoir (Figure 4B) are two members of this group.

A fifth group consists of cylindrical spring and slit-sleeve or ball valves. They are tubular to palpation, are of variable size and have hard metal ends. The Holter valve (Figure 5A) and the Hakim valve (Figure 5B) are two members of this group. They may be attached to perforable antechambers or reservoirs if inserted after 1969. The addition of an antechamber or reservoir allows for perforation for injection, aspiration or pressure recordings from the cerebral ventricles. Perforation of the tubular valve itself, however, may lead to leakage or damage to the valves and subsequent malfunction. With occlusive finger pressure on the valve, injection into or pressure on the reservoir or antechamber results in retrograde CSF flow toward the cerebral ventricle. Repetitive finger pressure on the soft midsection of these tubular valves pumps CSF toward the distal limb. Neither valve, if competent, allows CSF to flow retrograde toward the cerebral limb. A valve that depresses with difficulty indicates obstruction distal to the point of pressure.

Recently, the most complex and most easily distinguishable valve, the Heyer-Schulte Multi-Purpose Valve, has been introduced (Figure 6). It consists of four devices and includes an occluder, a device designed to prevent loss of proximal limb occlusion by external compression when bony overgrowth occurs, a reservoir, a differential pressure valve (Miter) with an on-off control, and an antisiphon device. The antisiphon device is a valve that prevents the excessive drainage of CSF during negative pressures and is particularly important in patients with inspiratory air-

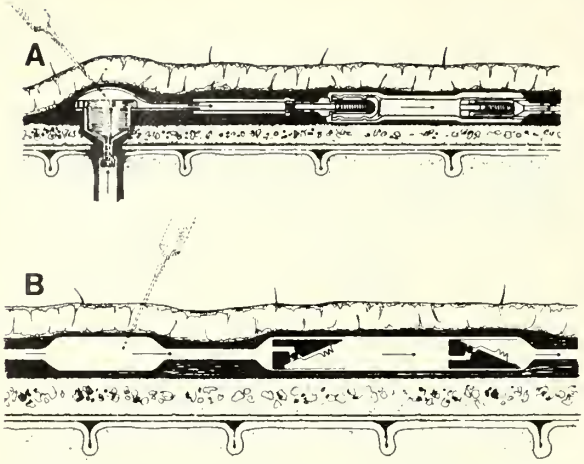

Figure 5.—Tubular One-Way Valves with Reservoirs. The reservoir and antechamber are safely perforable—the valves are not. **A,** Holter Valve with Rickham Reservoir. **B,** Hakim Valve and Antechamber.

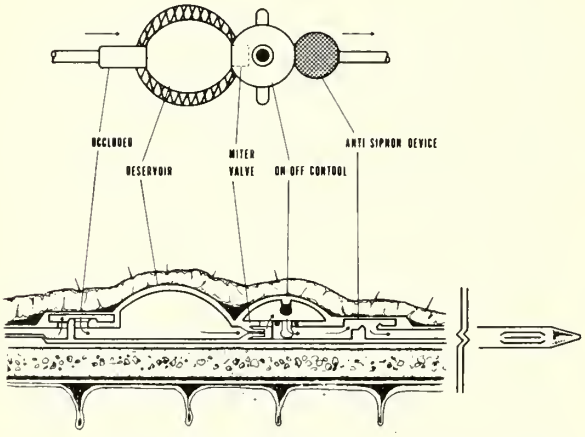

Figure 6.—Heyer-Schulte Multi-Purpose Valve. (Pictured with Pudenz One-Way Distal Slit Valve). The reservoir is safely perforable while the antisiphon device is not. The occluder prevents cerebrospinal fluid flow in both directions with external pressure and is more effective than tube compression. The Miter differential pressure valve as opposed to the Heyer distal slit valves is protected from changes secondary to body fluids. The on-off control is radiopaque. External pressure engages the button occluding cerebrospinal fluid flow. Finger pressure on the occluder with simultaneous pressure on the reservoir will "pop up" the button, thus allowing cerebrospinal fluid flow.

way obstruction and an intrathoracic distal shunt tip. Partial largyngeal nerve paralysis, resulting in inspiratory airway obstruction, is a frequent complication of the Arnold-Chiari malformation associated with the myelodysplasia-hydrocephalus complex.[10] It seems reasonable to expect that components of the "multipurpose" valve of the Heyer system, such as the occluder and antisiphon device, will be used in combination with other

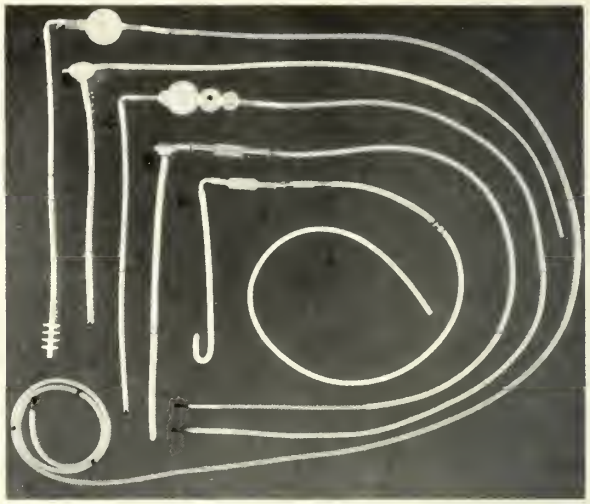

Figure 7.—Common CSF Shunt Systems. A, Foltz To and Fro Flushing Reservoir (two inlets) with MPF Ventricular and Raimondi Spring Peritoneal Catheters. The two inlet device is used when shunting from two areas is indicated. The MPF (multiperforated flange) ventricular catheter with its flanges and numerous perforations minimizes the chances of clogging while the embedded spring in the Raimondi catheter is designed to reduce kinking. **B,** Pudenz One-Way Flushing Reservoir with Standard Pudenz Ventricular and Infant Cardiac Catheters for use in infants with very small veins. **C,** Heyer-Schulte Multi-Purpose Valve with Standard Pudenz Ventricular and Peritoneal Catheters. **D,** Holter Valve and Rickham Reservoir with Standard Ventricular and Pudenz Infant Cardiac Catheters. **E,** Hakim Valve and Antechamber with radiopaque Curved Ventricular and Straight Drainage Catheters.

reservoirs and valves of various types in the future. Some of the more common cerebrospinal fluid shunt systems are pictured in Figure 7.

General Principles of CSF Shunt Systems

The various CSF devices are designed to (1) allow unidirectional CSF flow, (2) allow flushing of the distal shunt using increased pressure, (3) allow retrograde (ventricular) flushing of shunts, (4) allow intra-ventricular injections of therapeutic or diagnostic agents, (5) allow graded levels of CSF flow, (6) limit CSF flow during times of negative intrathoracic or intra-abdominal pressure and (7) allow for intermittent CSF drainage.

The one-way flow slit valves such as the Holter and Pudenz were originally developed to assure unidirectional CSF flow without reflux of blood or other body fluids. The Hakim ball-spring one-way distal flow valve was later developed to handle high protein and cell containing fluids, fluids not as well handled by the Holter and Pudenz valves. A number of devices have been

developed to allow for proximal or cerebral flushing or injection and are, therefore, safely perforable using a 25 gauge or smaller needle with strict aseptic technique. They include some Heyer units (Figures 2B, 3, 4, 6), the Rickham Reservoir attached proximally to the Holter system, and the "antechamber" portion of the Hakim valve system. Pressure gradients have been modified by altering spring strength (Hakim) or tubing thickness and compliance (Heyer, Holter and Miter) to allow high, medium or low pressure shunt valve openings.[2,3,7] A recent ingenious addition to shunt devices consists of a bottom plug which can shut off CSF drainage without operation (Figure 6).

The evaluation of shunt function is dependent upon the specific device. A firm or resistant chamber or dome generally indicates obstruction in one or both limbs depending upon the particular device. A dome that compresses but does not refill indicates flow of CSF distally or proximally, or both, but no or poor CSF flow from the cerebral ventricle toward the dome. A dome that returns to a full position with proximal occlusion indicates that the distal valve is incompetent, there is a leak in the device or tubing and the defect is surrounded by fluid, or proximal occlusion is not complete. A malfunctioning shunt per se, however, in the absence of clinical symptoms is not an indication for shunt revision as a significant number of persons with CSF shunts may be asymptomatic with "nonfunctioning" shunts. Sudden death, however, has been observed in a few of our teenage patients with an acute illness and a nonfunctioning shunt in an otherwise asymptomatic patient.

A clinician cannot always distinguish by palpation the type of device encountered since with time bone and connective tissues tend to obscure the distinguishable characteristics. In addition, certain materials used in devices tend to harden with time,[11] making identification and evaluation of function by palpation even more difficult. Barium impregnated catheters, tips and tubing, as well as the metal parts of certain devices make the identification by x-ray of certain devices possible[2,3,7,12] (Figure 8). Documentation of certain physical measurements may at times facilitate identification of certain devices.[13]

Discussion

Although comparative studies of the various shunt mechanisms have not been reported, the diagnosis, treatment and management of shunt obstruction and infection have been greatly facilitated by the development and improvement of such devices. The advantage of proximal shunt access allows for the direct installation of anti-

Figure 8.—Radiographs of Common Shunt Systems. Holter Valve **(left)** without Rickham Reservoir, Pudenz One-Way Flushing Reservoir with MPF Catheter **(center)**—tubing connectors are palpable but radiolucent, and Hakim Valve and Antechamber with right angle (proximal) and straight (distal to valve units) metal tubing connectors **(right).** All components are subcutaneous except the three partially radiopaque ventricular catheters. The radiolucencies in the center and right roentgenographs are due to small volume air contrast studies now generally replaced by safer and more informative computerized tomography and combined pressure and radionucleotide studies.

biotics into the ventricular system resulting in notably increased recovery rates from shunt-related infections.[14,15] Ventricular and distal shunt system access also allows for direct CSF pressure recordings and more recently for the evaluation of shunt patency and shunt dependency using radioisotope techniques.[16-18] The advantages gained by the use of the various shunt mechanisms available, however, must be weighed against the mechanical problems inherent in the more complex devices. Our policy is to use the simplest, softest available device that allows both direct cerebral ventricular access and distal access, as well as bidirectional shunt flushing.

Acute shunt obstruction and shunt-related infections can rapidly be fatal if unrecognized, untreated or improperly managed. The physician responsible for the care of children with CSF shunts must be familiar with these devices if he is to manage these patients intelligently. Intelligent management of shunt-related problems by primary care physicians, in addition to familiarity with shunt mechanisms, requires the availability of carefully documented and transcribed operative notes and hospital records of the exact type of shunt system involved. Physicians responsible for the daily care of these children should receive from the neurosurgeon full explanations for safely evaluating shunt patency and function. Parents and other persons concerned with the child's well-being should also be fully informed regarding the signs and symptoms of shunt-related problems as well as the function of the patient's device. Also, patients with CSF shunts should wear identification tags stating the type of their device.

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Traumatic Fibromyositis

A Critical Review of an Enigmatic Concept

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Traumatic fibromyositis is not an inflammation; there is no fever, leukocytosis or increased sedimentation rate; electrical characteristics and serum enzyme levels are within normal limits, and there are no observable pathologic alterations, although they have been carefully searched for. Recent attempts to express the effects of muscular sprain or strain as a biochemical disturbance expressed in an unusual pattern of lactate dehydrogenase isoenzymes appear not only to be technically flawed but inconsistent with results of conventional enzyme studies on other muscle and interstitial inflammations. In the author's view, "traumatic" fibromyositis is no more than a verbal construct arrived at by adding an adjectival modifier to the old terms for idiopathic rheumatic disorders. An examination of the evolution of the concept of traumatic fibromyositis shows that it lacks validity as a clinical diagnosis and ought to be abandoned.

"We do not add to knowledge by condensing our ignorance into a formula."
ELLIS*

TRAUMATIC FIBROMYOSITIS and cognate titles presumably define and describe an entity believed to follow trauma and expressed clinically by painful muscles, hardened bands or nodularities (or both), stiffness and spasm. These subjective complaints all occur without fever, leukocytosis, anemia, increased sedimentation time, muscular weakness, electromyographic abnormalities or increase in serum enzyme levels. Attempted explication of this ambiguous condition has summoned forth arcane but so far unverified hypotheses of autoimmune phenomena,[1] suspected involvement of the sympathetic nervous system,[2] involvement of the central nervous system,[3,4] as well as concepts of referred pain that ignore accepted boundaries of nerve distributions.[1,5-7] Pathophysiological explanations which invoke complex self-perpetuating or regenerative mechanisms have been imagined in order to account for the chronicity of the complaints and both for their obduracy to therapy as well as for their occasional tractability.[1,4,8-10]

Though it has been useful to physicians as a facile explanation for persistent and baffling complaints, "traumatic fibromyositis" appears to be an example of how a rheumatic malady, by the arbitrary insertion of a modifying adjective, was converted into an acceptable consequence of trauma. Such heedless wordsmithing not only leads to wide medical, legal and economic consequences, but inevitably invites disbelief. Lately, some investigators using the techniques of differential separation of lactate dehydrogenase iso-

*Remarks made to the Boston Society for Medical Improvement, January 26, 1880.

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enzymes have attempted to make the concept of "traumatic" fibromyositis legitimate by giving it a biochemical underpinning.[11,12] Because of our belief that traumatic fibromyositis is no more than a part of the folklore of trauma supported mainly by the subjective evaluations of physicians dealing with subjective complaints, a critical overview seems justified.

Origin of the Concept

In tracing the evolution—and mutation—of "traumatic fibromyositis," one returns more than a century to Froereip (1843) who originally described a rheumatic state[13] in which tender or hardened areas (or both) appeared in the muscles accompanied by pain, stiffness and sometimes by fever. The rich literature that followed has been summarized by Kraus[14] and by Simons.[15] While many conjectures were made concerning its nature, neither significant nor constant histiological alterations were shown in spite of numerous efforts.[16-22] For many decades, the condition paraded under different names: fibrositis, fibromyositis, myofascitis, myofibrositis, epidemic myalgia, myogelosis, muscular rheumatism, nonarticular rheumatism, painful myosis, tension rheumatism, psychogenic rheumatism, sensitive deposits, occupational myalgia and, lastly and lately, interstitial myofascitis.[11] In many instances, the signs and symptoms were probably confused with the phenomena of rheumatoid arthritis and other, but then unknown, collagen disorders. Sir William Gowers (1904) subsumed them all under the general rubric of fibrositis and supposed the cause to be an inflammation of the white fascias.[23] Kelly, 60 years later, resurrected this conjecture but added no additional evidence.[24,25] Max Lange (1931) in an influential book originated the concept of colloid or gel-like changes in muscle in order to explain the hardening, which he allegedly felt and measured with an instrument of his own design.[26] There has been no histological verification of his ideas. They fell into obscurity and now are only historical fossils. Although they repeatedly resurface in descriptions of, and speculations about, equivocal "muscle lesions," none of these are more convincing than the original efforts of Lange.[15]

Expansion of Theory and Treatment

Arthur Steindler (1937)[27] is credited with taking one aspect of the common complaints, namely the tender and painful areas—following an earlier suggestion of Edeiken and Wolferth[28]—and endowing them with the catchy sobriquet "trigger points."[27] He suggested injection with procaine solution to relieve the pain; henceforth, it became standard treatment. Possibly influenced by this success, Travell[6-8,29,30] in a series of papers not only devised a hypothesis to account for the trigger points, but, more important, introduced a speculation to explain the chronicity of the disorder. She asserted that self-perpetuating pain-spasm-pain sequences were due to the reciprocal complexing of several, but unspecified, nervous, environmental and exogenous influences.[31,32] Needless to say, these conjectures went unproved though her conclusions still influence treatment[5,6,33] and led to the introduction of the treatment with ethyl chloride spray.[35,36] As with most therapeutic suggestions, Steindler's innovation was carried further by others and injections of exotic agents into osseoligamentous attachments were employed in order to "relax" ligaments.[37] Many physicians, accepting the suffix "itis" as a therapeutic challenge, have administered steroids or injected them into the tender areas.[38] Other investigators injected the trigger points in 1,000 patients, with equivalent quantities of normal saline, and reported excellent results.[39,40] Indeed, the injection of miniscule amounts of saline[2] and sometimes multiple punctures with a dry needle have relieved complaints[29] equally well. Sola and co-workers[41] found that in approximately 50 percent of healthy uncomplaining recruits there were "latent" trigger points which were asymptomatic until prodded. This experience is seldom related to clinical practice.

Rheumatic Fibromyositis Evolves Into Traumatic Fibromyositis

The year after Steindler's paper appeared, a reference is noted in *Advances in Orthopedic Surgery*[42] which suggests that an unexpected conceptual mutation was taking place. Burns and Ellis[42] wrote respecting sprains that *"unless the area is rested, inflammatory changes are introduced and the pain becomes almost continuous . . . fibrositis is more likely to attack damaged or irritated tissues"* (italics added). Steindler and Luck[9,27] had also implied a traumatic cause. The idea that a muscular injury could be transformed into an inflammation was clearly a very attractive one. Therefore, the sharp warning of S. A. Kinnear Wilson[43] that the term myositis and its cogeners "should not be employed in connection

with trauma" went unheeded. Many textbook writers in the last several decades have accepted the concept of a "traumatic fibromyositis" so that even if it is only an unsupported verbal construct, it has been a persuasive one.[3,44-52] It has inspired several conferences on connective tissue,[29,53] an outpouring of papers and studies[15] and the development of therapeutic methods, but its proponents have failed to provide a coherent and validated set of observations that confirm fibromyositis to be either a consequence of injury or an inflammation.

While there is no doubt that patients complain bitterly of muscular aches and pains under the familiar designations of lumbago, wry neck or muscular rheumatism, as well as the list previously mentioned, none of these including "traumatic" fibromyositis have shown identifiable pathology and therefore (like the legendary unicorn, which all have hunted and none seen), the alterations implied by the name and supposed to underlie the symptoms have eluded the pursuit of expert microscopists.[54,55,57] Nor have adjunctive methods such as electrical studies, enzyme determinations, rheumatoid flocculation tests or studies of sedimentation rates shown substantiating abnormalities. Recently, Awad and his group,[11] following the lead of Brendstrup and associates,[57] who believed that they had found increased quantities of mucopolysaccharides in "fibrositic" muscles, have forced reexamination of the question by renaming fibrositis, "interstitial myofascitis," and stating that "the condition has one requirement, trauma." This blunt assertion was based upon findings in 32 patients who were selected for study on the basis of purely subjective criteria: subjective complaints of pain, subjective muscle tenderness, the presence of the "jump sign" (the patient flinches in a characteristic way from the examiner's palps)[38] and finally the examiner's subjective impressions of muscle consistency. Electromyograms were made and showed in six cases only polyphasic potentials—an equivocal result. However, Kraft and co-workers,[38] carefully examined 16 patients in whom equivalent diagnoses had been made and found electrical silence in all cases.

Based on findings from biopsy studies in 10 patients and from sera studies in 32 patients, Awad and co-workers[11] constructed an elaborate hypothesis suggesting a digressive—but sequential—connection between trauma and deposits of amorphous material described as lying among and between otherwise normal muscle fibers. Their pathogenetic theory consisted of a series of inferences resting upon inferences and bound by a number of conditional and anthropomorphic modifiers as follows: *Trauma leads to an extravasation of platelets which release serotonin causing vasoconstriction. This, then, leads to localized muscular edema which may result in degranulation of mast cells* (several such cells were seen) *and consequent release of histamine and heparin. The released histamine attempts to counteract the vasoconstriction and the heparin may prevent the clotting of extravasated blood and lymph. Aspirin relieves the symptoms because it inhibits the blood platelets; it is also postulated that aspirin inhibits the release of serotonin. The beneficial effects of heat are probably due to vasodilation; massage and ultrasound probably result in degranulation of mast cells by the mechanics of irritation.* These dubious and strained arguments are evidently thought adequate to forge a chain of causal links between trauma and the metachromatically staining amorphous material.

In a subsequent paper, Ibrahim and co-workers[12] attempted to support this theory by showing what they believed to be an abnormal pattern of distribution of the five lactic dehydrogenase (LDH) isoenzymes. They discounted the normal serum levels of LDH in their cases, although the total quantity usually not only measures the degree of tissue injury but exerts profound effects on isoenzyme distribution.[58-62] There were inexplicable variations in their figures for acute and chronic myositis although one would suppose them to be all the same disorder. Their technique of storing the entire biopsy specimen three days before mincing introduces errors[63,64] according to Everse and others. Their data and conclusions beg for substantiation since the authors appear to be describing a novel and hitherto unknown disorder of connective tissue characterized by agglomerations of interfascicular amorphous mucoid substances, but with unaffected muscle fibers, absent interstitial cellular reaction and a peculiar distribution of isoenzymes with normal serum LDH levels. Furthermore, their cases were cured by treatment with aspirin, heat and physiotherapy.

Modern myologists,[54-56] systematic pathologists,[65-67] orthopedic pathologists,[68] atlases on muscle pathology,[69] symposia on myology[70] and connective tissue[71-73] either do not mention "traumatic" fibromyositis or dismiss it as a nebulous

concept. Intensive studies of the nodularities about which so much has been written disclose on excision only herniations of fatty-fibrous tissue through fascial rents or nerve openings.* Bateman speculated[44] that these might cause inflammation and pain, but presented no affirmative evidence. Indeed, the existence of such a reaction as muscle inflammation due to trauma has been flatly negated by Betty Banker in a series of animal experiments.[75] Cutting, crushing, gunshot wounds and radiation did not provoke an inflammatory response; quite the opposite—abused muscle heals smoothly and blandly. Pearson and Rose[76] took specimens of ten muscles in each of 100 consecutive autopsies and found only one example of interstitial myositis; that in a case of known collagen disease. Surely, if the concept of traumatic fibromyositis is genuine, one might suppose that among these 100 silent testimonials, some of the patients had had enough trauma to have left a trace. This is especially so if there is any truth to assertions that the condition may become chronic.

Discussion

Notwithstanding the lack of histologic support, the concept of traumatic fibromyositis seems imprinted on the minds of many and will not easily suffer extinction. The vague and enigmatic entity has been exploited by psychiatrists who state that an actual physical injury, "fibromyositis," provides the organic nidus around which a "neurotic psychophysiological reaction" develops.[77] But specialists in arthritic disorders warn, concerning so called fibromyositis, that "its close relationship to a psychogenic origin should be kept in mind."[78] "Psychogenic rheumatism," a rather awkward conjunction of disparate terms, is a commonly accepted explanation for diverse symptoms.[80-82] Many rheumatologists[16,42,48] believe that the tendentious and monotonous complaints of muscle pain and tenderness either express a neurotic preoccupation with the body or are examples of hysterical body language.[83] Experienced physicians, agreeable to psychological explanation, who have listened to months of lamentations from patients with no objective evidences of injury, following small accidents, readily accept this explanation.[48]

Nevertheless, the reality of "traumatic fibromyositis" has been embraced by physiatrists who have created a large literature on the subject[15] and who treat it with many modalities and sometimes for long periods. More overt examples of muscle injury, such as that which follows wide retraction incident to laminectomy, do not receive a similar gamut of physiotherapies. These are more often used in the treatment of muscular sprains or strains following vehicular accidents or misadventures at work. If the same intractable complaints followed spinal operations, such surgical procedures could not be carried out.

A large part of the reason why traumatic fibromyositis continues to be a popular disorder derives from the eagerness with which many patients submit to protracted—and sometimes painful—physiotherapy because of the suggestive influence of a medical diagnosis and the respectability it bestows upon otherwise puzzling and unaccountable complaints.[84] An overview of the history of "fibrositis," spontaneous or traumatic, suggests that it is no more than a medicalization of the common aches and pains of mankind. Inasmuch as "disease" is what medical men say it is, long ago it was assumed that some muscular "disease" underlay the variegated but common symptoms. Later this was extended to the effects of trauma. In the last half century, there have been vigorous attempts to justify this propensity with acceptable evidence, all of which, in the reviewer's opinion, is unconvincing or has not held up. The recent contentions, microscopic and biochemical, alluded to earlier, are either unverified or incompatible with accumulated knowledge of muscle disease, myositis or interstitial inflammation. It exceeds credence to accept the concept advanced by Awad and Ibrahim and their co-workers that local strains or sprains of muscles affect enough tissue bulk to produce peculiar shifts in isoenzyme distribution without causing increase in serum levels of LDH.[59-63] The older literature seems only to be theory put to the service of explaining symptoms and is full of conflicting diagnostic, therapeutic and theoretical claims. It seems apparent that traumatic fibromyositis should be regarded as one of the many medical myths making up the folklore of trauma and therefore should be discarded as a serious clinical diagnosis.

*17,18,21,22,74

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Specialty Conference

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The Management of Diabetic Acidosis

WILLIAM L. NYHAN, MD, PH D:* *Diabetes mellitus is the most common endocrine disease in childhood as well as the most common metabolic disorder. There are more than 200,000 children with diabetes in the United States. The management of the acute ketotic episode is an important component of pediatric emergency medicine. We shall illustrate this problem by the presentation of two patients. The first will be presented by Doctor Fonseca.*

ROBERT FONSECA, MD:† This was the first University Hospital, San Diego, admission for a 3½-year-old white girl who entered with a chief complaint of stupor. Four weeks before admission she had had chickenpox. At that time polydipsia and polyuria began, followed by increasing malaise. One week before admission nocturia began to occur, four to five times per night. Three days before admission she had gone with her parents to Baja California, where she refused to eat and started vomiting. She was treated with dimenhydrinate (Dramamine®) but did not improve. On the night before admission the patient became severely lethargic, refused all food and fluids, and was noted to have dark, sunken eyes. She tried to walk and collapsed in a chair on the morning of admission. She was flown by private aircraft to San Diego and brought by ambulance to University Hospital. On arrival she had no measurable blood pressure. Blood pressure was rapidly reestablished by intravenous administration of Ringer's lactate and salt-poor albumin.

On physical examination, the temperature was 36.9°C (98.4°F). Respiratory rate was 33 and pulse 140 per minute. Blood was 100/40 mm of mercury. She weighed 29 pounds. She was thin, pale and lethargic; was arousable, and responded groggily to pain and commands. The skin had poor turgor. The eyes were sunken. The oral mucosa was dry and the tongue parched. Acetone was noted on the breath. Urine reaction for glucose was 4+ and there were large ketones. The initial blood glucose level was 760 mg per 100 ml and acetone was present in the blood. A diagnosis of diabetes mellitus was made.

The initial push of Ringer's lactate was 10 ml per kg of body weight in half an hour, and it was followed by 0.5 grams per kg of salt-poor albumin. This brought the blood pressure up to 128/80 mm of mercury. Kussmaul respirations, 35 to 40 per minute, were noted. At this point treatment was started with approximately one-half isotonic saline solution at 200 ml per hour, which was calculated to replace the fluid deficit over the next eight hours. After the patient had urinated, 40 mEq of potassium phosphate were added per liter of intravenous fluid. After half an hour a continuous insulin drip was started,

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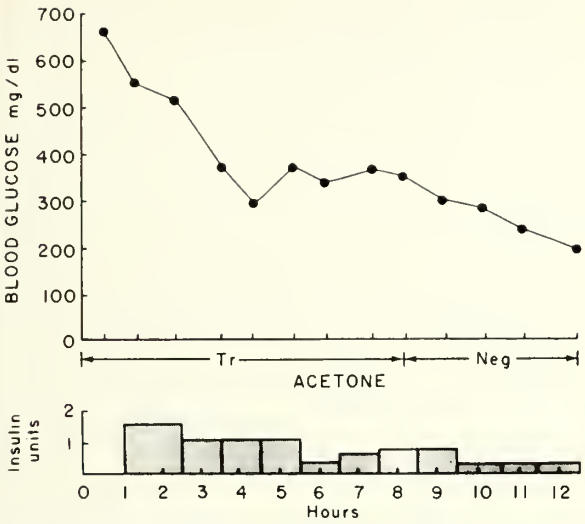

Figure 1.—Response of blood glucose in the first patient to continuous infusion of low doses of insulin.

following an initial push of two units of regular insulin, which was approximately 0.1 unit per kg. The drip provided 1.5 units of insulin per hour, which is equal to 0.1 unit of insulin per kg per hour. Within seven hours the blood was negative for acetone. The blood glucose value had dropped from 760 mg per 100 ml to 300 mg per 100 ml (Figure 1). After eight hours the rate of intravenous infusion was decreased to 50 ml per hour, which would supply the 24-hour maintenance fluid over the next 18 hours. Twelve hours after the insulin drip was started, the blood glucose value was 176 mg per 100 ml and the blood was negative for acetone. The infusion was stopped and the child was given 0.25 unit per kg of body weight of regular insulin subcutaneously. Every four hours injections of regular insulin were given, the doses determined by the blood and urine glucose values. After 48 hours, administration of a combination of regular and neutral protamine Hagedorn (NPH) insulin was begun. She was discharged two days later.

DR. NYHAN: *Thank you. The next patient will be presented by Dr. Nancy Morse Kaufman.*

NANCY MORSE KAUFMAN, MD:* The patient, a 10-year-old Mexican-American girl, was admitted in diabetic ketoacidosis. Diabetes was first diagnosed when she was 4 years old. Since then she had been admitted to hospital six times for acidosis and there had been at least one hypoglycemic seizure. For the previous year she had not been under close medical supervision. At the time of admission she had been receiving 32 units of regular insulin, and 48 units of NPH insulin daily. Five days before admission a flu-like syndrome developed which progressed to persistent vomiting. On the morning of admission a urine analysis showed a 4+ reaction for sugar and large acetone, so her mother gave an extra 10 units of regular insulin. Her condition failed to improve and she was brought to the emergency room.

On physical examination, the child was thin and restless. Kussmaul respirations were noted. Heart rate was 140 per minute, temperature 36.2°C (97.2°F), blood pressure 120/80 mm of mercury and the weight 69.5 pounds. The skin was cool and dry to the touch. The tympanic membranes were dull and red bilaterally. Her pharynx was mildly congested. She was lethargic but responsive, and her deep tendon reflexes were symmetric.

Admission laboratory data showed a blood glucose value of 600 mg per 100 ml with trace serum acetone. The carbon dioxide level was 4, sodium 128, potassium 5.9 and chloride 95 mEq per liter. The leukocyte count was 35,900 per cu mm, hemoglobin 14.5 grams per 100 ml and hematocrit reading 43 percent. Initial blood gas analysis showed a pH of 7.21 with a carbon dioxide pressure of 15. Urine had 4+ reaction for glucose and a large amount of acetone.

An intravenous infusion was started and Ringer's lactate with added potassium to make 40 mEq per liter was given. As soon as the blood glucose value was known, she was given an initial dose of one tenth of a unit of regular insulin per kg of body weight by intravenous push, and then a continuous infusion of insulin was begun at a rate of 0.1 unit per kg per hour. This was continued for 2½ hours, at which time the blood glucose concentration was 242 mg per 100 ml and the urine was negative for acetone. The subsequent rate of infusion of insulin was regulated on the basis of hourly determinations of blood concentrations of glucose. In addition, the child was given appropriate fluids for dehydration. The drip was discontinued after 8½ hours, at which time the blood glucose value was 162 mg per 100 ml. The child received a total of 15 units of insulin via the drip, plus the three units which were given by intravenous push before the drip was begun. The remainder of the hospital course was uncomplicated. She was managed with regular

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insulin every four hours for the next day and a half, and was discharged on a dose of 20 units of regular and 44 units of NPH insulin.

DR. NYHAN: *The course of these two children was really very rewarding. I believe that this approach, the continuous low dose intravenous infusion of insulin, is the first real advance in the management of diabetic ketoacidosis in the past 30 years. We shall now ask Dr. Irvin Kaufman to discuss it for us.*

IRVIN A. KAUFMAN, MD:* The first clinical description of diabetes was made by the Greek physician Aretaeus the Cappadocian in the first century, AD. He believed diabetes was a melting down of flesh into urine. Fifteen hundred years passed before Sir Thomas Willis noted the sweetness of diabetic urine and added the term mellitus (honey-like) to the designation of the disease. Starling was the first to suggest in 1920 that the pancreas secreted a hormone that enabled tissues to utilize glucose, and the following year Banting and Best extracted insulin from the pancreas and showed its blood glucose lowering properties. The first patient was treated with insulin within a year of this discovery.

In a nondiabetic person there is a biological balance between insulin and its antagonists, growth hormone, catecholamines, glucocorticoids and glucagon. In a diabetic, or insulin deficient state, the actions of these antagonistic hormones are unopposed, and this results in a catabolic state. Normally, insulin acts to inhibit lipolysis, sparing adipose tissue from breakdown. It also blocks gluconeogenesis by inhibiting hepatic enzymes, sparing protein from breakdown. In addition, insulin augments the transport of small molecules, such as amino acids and glucose, across cell membranes. It also augments glycogen synthetase and inhibits phosphorylase, promoting glycogen storage. In a diabetic state, lipolysis and ketone formation are unchecked. Protein is broken down, glycogen stores depleted, and glucose uptake by cells diminished. The net effect is similar to starvation. Before the discovery of insulin, most children with diabetes died in ketoacidosis. Today with advances in management, current mortality in children is less than 1 percent in most centers. However, diabetic ketoacidosis remains a medical emergency. It must be recognized and treated promptly, or death can result. Many different regimens have been proposed for the treatment of diabetic ketoacidosis. Most have been highly empiric.

There have been many different approaches to the insulin therapy of diabetic ketoacidosis, and there are continuing disagreements on both the size of the initial dose and the route of administration. In general, a large initial dose has been advocated. The usually suggested dose has beeen 2 units per kg of body weight,[1] but as much as 3 to 4 mg per kg has been recommended.[2] A portion of the initial dose has been given intravenously and the remainder subcutaneously. Subsequent doses have usually been given at two to four hour intervals subcutaneously. An argument was provided in the *Journal of Pediatrics* in 1973[3] for considerably lower doses of insulin on the basis of experience with some 44 patient episodes. An assessment was made of how much insulin it took, if it was decided not to give a large dose, to achieve a defined level of recovery, such as how much it took to reach a state in which the serum bicarbonate level was 20 mEq per liter, or greater. In this series of patients, it took about 0.5 unit per kg. The interval required to achieve this was approximately 11 hours. These are reasonable goals. If they can be achieved with 0.5 unit per kg one wonders why more would be used. In an editorial in the same issue of the *Journal of Pediatrics,* Weil[4] wrote that he failed to see any real advantage in utilizing as little insulin as possible. We do not agree. Insulin certainly is not devoid of toxicity.

We no longer do growth hormone stimulation with insulin because severe hypoglycemia and seizures can develop. It is also true that in the long-term management of patients with diabetes there are many more episodes of hypoglycemia due to overinsulinism than of diabetic ketosis. In initial stabilization of an acidotic diabetic patient in the hospital, using the old high dose regimens, a pattern frequently emerged. In a patient who is notably ketotic and at the same time has a blood glucose level of say 500 mg per 100 ml, large amounts of insulin are given subeutaneously and four or six hours into treatment the patient has a blood glucose level of maybe 75 or 50 mg per 100 ml, or even lower, and no urine sugar, and yet is still notably ketotic. This situation can be handled giving more insulin along with adequate amounts of sugar. Often insulin is withheld for a number of hours as the patient returns to a ketotic hyperglycemic status resembling that on admission. The

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treatment of diabetes is directed against the cellular metabolic defect and ketosis as well as hyperglycemia is an index of the fact that the fundamental defect is an absence of insulin. These considerations all argue for using less insulin rather than more.

A look at the evidence supporting large doses of insulin provides little rationale for their necessity or desirability. Findings in two retrospective studies from the 1940's showed a lower death rate among patients who received relatively higher doses of insulin.[5,6] However, the groups who had received the lower doses had been treated as long as 20 years before those receiving the large doses, during which time there were many other changes in therapy including antibiotics and improved fluid and electrolyte management. Another reason given for the use of large doses of insulin has been the concept that acidotic patients are relatively resistant to insulin. Recent work has cast considerable doubt on this concept. Hockaday and Alberti[7] found no differences in sensitivity to insulin in a series of patients who had a range of pH values from 6.90 to 7.30. They pointed out that if resistance is defined as fall in blood sugar per hour per unit of insulin, factitious resistance can readily be seen whenever a supramaximal dose of insulin is given. Christensen and Orskov[8] have shown that there is a transport maximum (T-max) for glucose at serum concentrations of insulin of 200 μU per ml. This level is greatly exceeded in the usual high dose management of diabetic acidosis with insulin. Furthermore, the half-life of insulin in serum is very short, on the order of 3 to 4 minutes. Consequently, within 25 minutes following an intravenous bolus of insulin, serum levels will be back to basal values. The use of intravenous boluses alone or in combination with subcutaneous insulin administration may leave gaps in coverage, even with enormous doses. Subcutaneously given insulin may have slow, variable and unpredictable absorption—especially in a volume-depleted patient.

The continuous infusion of low doses of insulin for the treatment of diabetic acidosis appears to have a sounder basis in the physiology and pharmacology of diabetes. Although this method was used as early as 1960 and shown to be safe and effective, it did not apparently have wide-spread acceptance and the technique had to be rediscovered by Sonksen and associates in 1972.[9] They suggested that maintaining a steady-state concentration of insulin by means of a continuous infusion would provide better management for severely ill diabetic patients. Studies, mostly on adults, from a number of centers in Great Britain and Australia employed regimens of low dose continuous intravenous administration of insulin. Page and colleagues[10] treated 38 patients successfully with an average of 6 units per hour. Plasma concentrations of insulin were maintained in the range of 50 to 200 μU per ml. Serum concentrations of glucose and ketones fell steadily. The rates of recovery were not slower in these patients than in those treated with doses of insulin ten times greater. Hypoglycemia and hypokalemia were not problems in these patients.

Kidson and colleagues[11] reported good results with infusion rates of 2.5 units per hour. Serum levels of insulin of 40 to 80 μU per ml were achieved. The therapeutic effect was not greater with higher infusion rates. The rate of fall of the blood glucose was roughly linear, but it did not correlate with serum insulin levels within the therapeutic range of 50 to 200 μU per ml.

Since we adopted this technique[12] it has been used successfully in approximately 30 patients at Children's Hospital and Health Center, University Hospital, Mercy Hospital and the United States Naval Regional Medical Center, in San Diego. The youngest patient treated was 9 months old. The highest blood glucose value was 2,000 mg per 100 ml. Several patients were severely acidotic with pH values less than 6.90. Our protocol for the use of this method in children is laid out in Table 1. The course of the blood glucose response to treatment in a patient on this regimen is shown in Figure 1. There are a number of clear advantages to this method of low dose continuous intravenous infusion of insulin. It provides a steady serum concentration of insulin in the effective range, avoiding the peaks and valleys in serum insulin that are the rule with intermittent dose regimens. When the steady state is reached after the initial fall that is due to rehydration, the blood concentration of glucose falls at a linear rate of 70 to 100 mg per 100 ml per hour. This permits physicians to anticipate changes in blood glucose values and the need for the addition of glucose to the infusion. Because the half-life of insulin in blood is short, serum levels can be altered quickly by speeding up or slowing down the rate of infusion. After an infusion has been stopped, the serum concentration of insulin returns to basal levels in ten minutes, and no further fall in plasma glucose is seen. This fact, to-

TABLE 1.—*Treatment of Diabetic Ketoacidosis with Continuous Intravenously Given Low Dose Insulin*

1. Initial blood studies should include determinations of glucose, electrolytes, blood urea nitrogen, blood gas for pH, serum acetone before therapy.
2. Prepare insulin infusion: Add 2.5 ml of 25 percent albumin to 250 ml of isotonic saline. Then add 50 units of regular insulin to the bottle. Shake gently. Each 5 ml contains 1 unit of regular insulin. Make a new insulin, albumin, saline solution every six to eight hours.
3. Fluid therapy should follow the usual guidelines and depends on the individual degree of dehydration of each patient.
4. Calculate insulin dose per hour as 0.1 unit per kg per hour. Give an intravenous push of regular insulin equal to 0.1 unit per kg. Then start insulin infusion by "piggyback" of the solution into the infusion of the replacement fluids with an IVAC pump. Maximum rate of infusion = 8 units per hour to start.
5. During the infusion, monitor glucose hourly, pH every two hours until normal, potassium every two to four hours and electrolytes as often as determined by clinical condition. Keep a flow sheet to include rate of insulin infusion as well as these lab values.
6. Plot blood glucose versus time on graph paper. Since glucose falls approximately linearly at a constant infusion rate, this will be helpful in predicting glucose values.
7. Add enough glucose to the intravenous solution to make it five percent, when blood glucose reaches 300 mg per 100 ml.
8. When the blood glucose level is 250 mg per 100 ml:
   - If the patient remains acidotic, and the acetone has not cleared, continue giving insulin at 0.05 to 0.1 unit per kg per hour and give sufficient glucose to keep serum glucose between 200 and 300 mg per 100 ml, that is, 2 to 5 grams glucose per unit insulin.
   - If serum acetone has cleared, or the serum pH has returned to normal, discontinue the infusion and manage the patient with subcutaneous administration of insulin given at intervals no greater than six hours. An initial dose of subcutaneously given insulin should approximate the total dose of insulin received over the previous four to six hours or approximately 0.25 unit per kg. The subcutaneously administered insulin should be given just before the insulin infusion is stopped.

gether with the predictable rate of decline, should make the risk of hypoglycemia negligible. The method is simple to administer and control, and it frees physicians from many empirical decisions regarding the dose, frequency and route of administration of insulin. It is more physiologic. Serum insulin levels approximate those of normal nondiabetic persons and do not grossly exceed maximum effective levels.

Another advantage of this method is that it should not unduly interfere with potassium balance. These patients all come to treatment with a deficit of potassium and if they receive very large doses of insulin—even if they receive enough glucose to avoid hypoglycemia—they must lay down a certain amount of potassium with the glycogen, and there is a rapid movement of potassium into cells. This can produce symptomatic hypokalemia, including cardiac arrhythmias.

It is also a real advantage of this system of management that it gives physicians a very specific end point to monitor. We are after a rate of decline of blood glucose, a chemical that is readily measured quantitatively in every clinical chemistry laboratory. This avoids the uncertainties of basing decisions on the urinary glucose or ketones, or the ketones of the blood, none of these very precise measures in clinical practice. With this system of intravenous administration of insulin, the blood glucose level is examined every hour. If it is not dropping by 75 to 100 mg per 100 ml each hour, something is wrong. This kind of immediate feedback makes management very much easier and safer. In Figure 1 the average decline of blood glucose was 100 mg per 100 ml per hour. These are the responses one would expect to physiologic amounts of insulin.

The addition of the albumin to the infusion mixture is to prevent insulin loss by sticking to the bottle and the tubing. Another, less expensive, approach to this is to utilize more concentrated solutions of insulin, but this may be dangerous in the management of infants and small children.

DR. NYHAN: Many of us who have grown up treating patients in acute-care hospitals, particularly in large city and county hospitals, have felt that most pediatric patients with diabetes present first in severe acidosis with a life-threatening illness. The literature does not support this. In the United States the frequency with which children with diabetes present for the first time in ketoacidosis varies from as low as 18 percent to as high as 50 percent. This means, of course, that at least half of the patients with diabetes present first in some other fashion. On the other hand, our text for this conference is the child who presents with acute ketosis and acidosis. An important element in the management of the patient is the provision of adequate quantities of fluid and electrolytes.

The pathophysiology of the derangement of water and electrolyte balance in diabetic acidosis depends in the first place on an absence of insulin, which sets everything else in motion. We

should assume in the management of pediatric patients that there is no insulin coming out of the pancreas. The effect of this on the utilization of carbohydrate is manifest most prominently in the hyperglycemia. This produces the massive osmotic diuresis that permitted diabetes to be recognized as such by physicians in ancient Greece. The increased filtered glucose exceeds reabsorption maximums, and this solute diuresis leads to large losses of water and electrolytes. The other issue is that of ketosis. This metabolic derangement is a consequence of the lipolysis that results from a lack of insulin in the presence of glucagon and leads to accumulation of acetyl coenzyme A (CoA) in amounts in excess of what can get into the citric acid cycle and be metabolized. When acetyl CoA accumulates it condenses with itself to form acetoacetate. It is this compound that breaks down to form the acetone that we measure when we test for ketones in the blood or urine. Therefore, the problem when a patient is ketotic is not that he has acetone in the blood—it is that he has acetoacetate. This is ionized in the plasma and the urine, and, as it is excreted by the kidney, it is excreted along with sodium and potassium. Furthermore, if we measure organic acids, we find that for every mole of acetoacetate in the urine or the blood of a ketotic patient, there may be many moles of β-hydroxybutyrate, and this is not a ketone, and consequently it is not measured when we test for ketones. In the presence of all of this extra acid that we do not measure, it is more useful to employ pH and serum bicarbonate studies to assess the patient's level of ketosis. In short, it is both the osmotic diuresis induced by excessive amounts of glucose and the accumulation of organic acids that lead to losses of water and electrolytes and to systemic acidosis. The altered physiology leads to dehydration and also there is a certain loss of calories and a metabolic starvation.

The most important consequence of dehydration to consider is that it leads to shock. The first patient presented had no measurable blood pressure on arrival at the hospital. This is a relatively common occurrence in pediatric patients presenting with diabetic acidosis. Such a patient is in shock because he is oligemic. The oligemia that results from losses of water and electrolytes through the kidney is no different in terms of its pathophysiological consequences from the shrinkage of the vascular volume that results from blood loss. It is the diminished perfusion of the tissues that ultimately leads to death. This is important for us to recognize in planning therapy. Our first consideration should be the restoration of the patient's volume, and the sooner we do this the better off the patient is. We repair the deficits in sodium and water in the first eight hours of treatment. We undertake an initial volume expansion with 20 ml of Ringer's lactate per kg of body weight or isotonic saline solution whether or not the patient is in shock and this is completed within the first hour. This is continued until blood pressure and circulation are restored in a patient who presents in shock.

TABLE 2.—*Losses of Water and Electrolytes in Severe Dehydration*

	H_2O mg/kg	Na mEq/kg	K mEq/kg	Cl mEq/kg
Diabetic acidosis	100-120	8-10	5-7	6-8
Diarrhea	100-120	8-10	8-10	8-10
Pyloric stenosis	100-120	8-10	10-12	10-12

The losses of water and electrolytes in patients with diabetic acidosis are shown in Table 2. These patients have an isotonic dehydration. The losses of sodium and water are proportional so that the concentration of sodium in extracellular water is normal. Therefore, although there are massive losses of sodium there is no way to examine the concentration of sodium in the serum and calculate how much to give. The same is true for the concentration of bicarbonate in the serum. In order to calculate how much water and electrolytes are missing from the patients we have gone to the literature in which actual balances were done to determine these losses. In diabetes these figures were obtained in a classic study[13] on patients in whom acidosis developed following insulin withdrawal while under study. It is interesting in Table 2 to see that in very different diseases that lead to dehydration, the losses of sodium and water are the same. This permits us to examine the patient and decide on his degree of dehydration, whether it is 5 percent or 10 percent or 12 percent. This then gives us the amount of sodium the patient has lost. A patient who is 10 percent dehydrated has lost 100 ml per kg of body weight. We assume for purposes of treatment that he has lost 9 mEq of sodium per kg of body weight. Our concept in deficit therapy, or the repair of dehydration, is simply that once we know how much sodium and water are missing from the patient we provide precisely that amount, and he should be back to normal.

TABLE 3.—*Schedule of Fluid and Electrolyte Therapy in the Management of Diabetes*

Time (hours)	Diabetic Acidosis: Solution	12 percent Dehydration: ml/kg	Na mEq/kg	K mEq/kg	Cl mEq/kg
0-1 ..	Ringer's lactate	20	2.6		2.2
1-8 ..	D_5W—40 ml Ringer's lactate—60 ml KPO_4—3 mEq/kg Maximum of 40 mEq/l of K+	100	7.8	3	6.6
Totals		120	10.4	3	8.8

The same approach cannot be taken with potassium therapy. Potassium is too toxic to attempt to provide the entire deficit in the time interval in which we would like to repair the sodium and water deficits. Also, it is predominantly an intracellular ion and even in balance studies where an excess was provided, only a certain amount was retained each day. Therefore, in potassium therapy we are guided by maximal safe limits. We employ 3 mEq of potassium per kg of body weight in the course of deficit therapy. This permits completion within eight hours at a rate of potassium administration 0.5 mEq per kg per hour. Table 3 provides a timetable for the management of fluid and electrolyte therapy in diabetic patients. It describes the management of a severely ill patient who is 12 percent dehydrated. In this program once the deficits have been provided the patient's condition is reevaluated. If the calculations have been made correctly and there are not large continuing losses, the patient will have been rehydrated, and maintenance therapy may be initiated. The first day's maintenance is given in 16 hours.

In the management of diabetic patients we provide potassium as the phosphate. We know that there are large deficits of phosphate in diabetes.[14] Serum phosphate concentrations tend to fall along with potassium following the initiation of treatment with insulin, possibly related to the deposition of glycogen. Phosphate depletion leads to a deficiency of 2,3-diphosphoglycemic acid (2,3-DPG) in erythrocytes. 2,3DPG is important in the affinity of hemoglobin for oxygen. Adequate amounts of 2,3DPG promote the release of oxygen to the tissues.

We have said that the usual patient with diabetic acidosis has isotonic dehydration. Yet in patient number two there was a serum sodium concentration of 128 mEq per liter and in many such patients there are concentrations of sodium considerably lower that that. There are a variety of reasons why a patient with diabetic ketosis might be hyponatremic, but in actuality they almost never are. I have never seen a patient with symptomatic hyponatremia in diabetic acidosis. It is a general rule that such a patient should never be treated with hypertonic salt in an attempt to correct the apparent deficit in concentration. Osmolarity is the important issue. A patient in nonketotic hyperosmolar diabetic coma with a blood glucose value of 1,800 mg per 100 ml has some 10 milliosmoles per 100 ml, or 100 milliosmoles per liter that are due to glucose. In such a patient the body cannot lower the sodium level to maintain normal osmolarity. If we measure the serum concentration of sodium in such a patient it will be normal or elevated. On the other hand, patients who are ketotic have a low serum concentration of sodium because they are hyperlipemic. This is factitious hyponatremia. The concentration of sodium in the serum water of a patient who is hyperlipemic is perfectly normal. However, in a person who is notably hyperlipemic there is a reduced concentration of water in the plasma, and when we measure the serum sodium which is only present in the water, the value we get back expresses the whole serum as the denominator with all its lipid, nonwater and nonsodium containing solids included. These considerations are relevant to any patient who is hyperlipemic. They can be very important in a patient with nephrosis.

A discussion of the management of diabetic acidosis must address the issue of bicarbonate therapy. This problem was elucidated by the work of Plum and Posner[15,16] who monitored the pH in the cerebrospinal fluid of patients treated for diabetic acidosis with sodium bicarbonate. Their fundamental observations were that when a patient is notably acidotic as shown by the pH in the blood, the cerebrospinal fluid (CSF) pH is normal, but as the patient is treated, the blood pH rises and the CSF pH falls. The other thing that clearly happens is that the carbon dioxide pressure in the CSF increases. People with acidosis, if they are not too ketotic or in shock, are by and large very sick, but conscious, and this can be related to the fact that the CSF pH is usually normal. On the other hand patients with respiratory acidosis are generally in coma, even with much less acidosis, and that is related to the fact that they have an acidosis of the central nervous system. The mechanism has to do with the relationship of bicarbonate to carbon dioxide (Table 4). Bi-

TABLE 4.—*Effects of Sodium Bicarbonate in Diabetic Ketosis*

Initial state
- Blood pH low. Cerebrospinal fluid pH normal or high. pCO_2 and HCO_3^- low in each.

Infuse $NaHCO_3$
- $HCO_3^- + H^+ \leftrightarrows H_2CO_3 \leftrightarrows H_2O + CO_2$
- CO_2 pressure in blood increases and CO_2 diffuses into central nervous system.
- HCO_3^- is nondiffusable—does not increase in cerebrospinal fluid.

Cerebrospinal fluid dependent on $\frac{HCO_3^-}{CO_2}$ buffering
- Raise CO_2 and pH falls.

carbonate is an efficient buffer but it does not pass across the membranes that separate the blood from the CSF. This protects the CSF of the acidotic patient where bicarbonate is concerned. In repair, if one infuses bicarbonate to a patient who is acidotic, the bicarbonate (HCO_3) is converted to carbonic acid (H_2CO_3) and this will release carbon dioxide, which diffuses readily into the CSF. Once in the CSF, carbon dioxide forms H_2CO_3 and CSF acidosis develops. There is very little protein in the CSF. Its pH depends virtually entirely on the bicarbonate to carbon dioxide ratio. This is a very strong argument against the administration of bicarbonate to these persons. An additional argument against the use of bicarbonate is that rapid correction of blood pH before the restoration of blood volume and adequate peripheral perfusion will offset the beneficial effect of acidosis on the hemoglobin-oxygen dissociation curve. The effect of depressed red cell 2,3DPH in diabetes is offset by the acidotic state. However, if sodium bicarbonate is administered and the pH rises, this protective effect is lost and a sudden increase in the affinity of hemoglobin for oxygen may produce hypoxia in tissues and a sudden deterioration in the patient. Abrupt increase in pH may also lead to symptomatic hypokalemia. From a number of large controlled series comparing diabetic patients treated with and without bicarbonate, it appears that supplemental bicarbonate does not materially improve the clinical course of patients with diabetic ketoacidosis. Since it may be harmful, it appears to make sense not to use it. Certainly there is a significant fall in the CSF pH in bicarbonate-treated patients. There is a special prohibition against using undiluted 7.5 percent sodium bicarbonate solution. This contains approximately 900 mEq per liter of sodium and 1,800 milliosmoles per liter. It provides a significant source of hyperosmolarity for a patient already hyperosmolar. Fatality has been observed.[1]

Physicians who have learned to treat diabetic acidosis with sodium bicarbonate worry that the altered acid-base balance may not be corrected using balanced salt solutions as outlined in Table 3. The point, as illustrated by both cases presented, is that if you provide a patient with the amounts of water and electrolytes he has lost becoming dehydrated and acidotic, the acidosis will be corrected along with the dehydration.

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Refer to: Insulin receptors: New insights into old problems—Medical Staff Conference, University of California, San Francisco. West J Med 127:112-119, Aug 1977

Insulin Receptors: New Insights Into Old Problems

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and Robert C. Siegel, Associate Professor of Medicine and Orthopaedic Surgery, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *Diabetes mellitus is perhaps the most important metabolic disease in the United States today. The discovery of insulin more than 50 years ago gave initial promise that the disease was at least explained pathogenetically and that the ultimate therapeutic tool was at hand. As we all know both of these expectations have been shown to be premature. It is remarkable that a half century of research still leaves insulin as clarified in structure but obscure in function, at least at the molecular level.*

Hormones must function by interaction with cells. Attention has recently been turned to the events of that surface interaction. Dr. Ira Goldfine has been an active investigator in this field and will review for us the current status of our understanding of insulin receptors.

DR. GOLDFINE:† Today, I will talk about an exciting new area of insulin action and diabetes mellitus, the recent direct studies of the binding of insulin to receptors in target tissues. As you are undoubtedly aware, significant progress has been made in understanding the biochemical mechanisms involved in certain states of primary and secondary diabetes. I believe, however, that it is appropriate at this point to give a few words of caution concerning studies in this field. It has been said that searching for the cause of diabetes mellitus is somewhat like the peeling of an onion, not only can the process bring tears to the eyes, but after each successful step, one is still left with the layer beneath. With this in mind, I will first discuss theoretical mechanisms of insulin action. Next, I will talk about the status of insulin receptors in states of primary and secondary diabetes. Finally, I will say a few words about possible future studies.

The Mechanism of Action of Insulin

Insulin is a relatively small protein comprised of 51 amino acids in two polypeptide chains, an A chain and a B chain, connected by two disulfide

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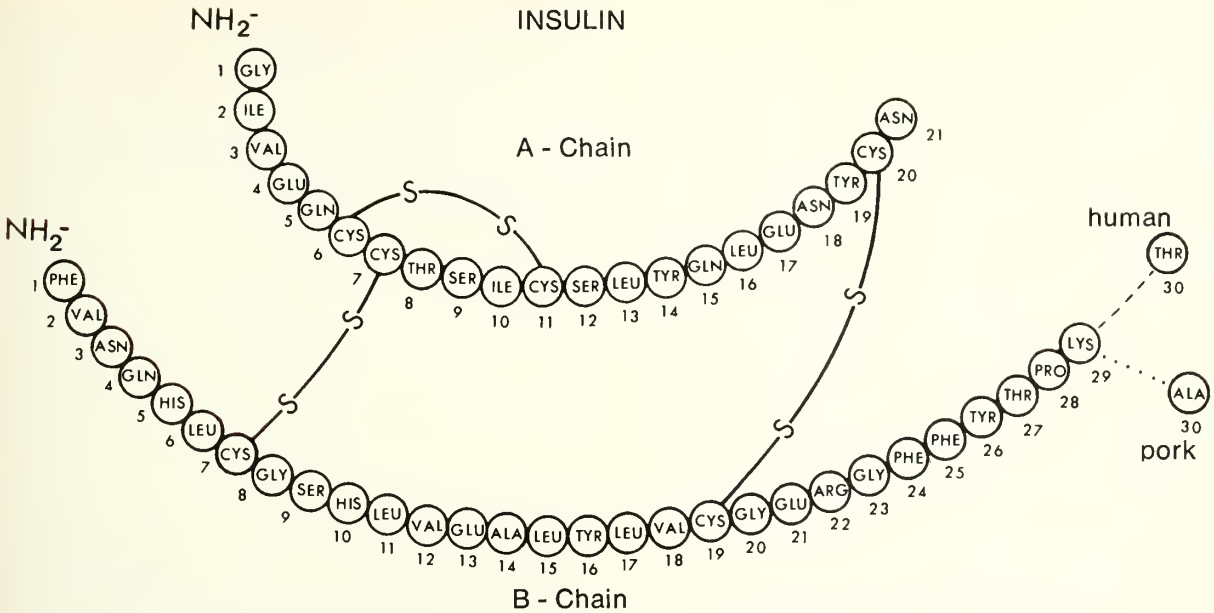

Figure 1.—The amino acid sequences of human and pork insulins. Note that they differ by only one amino acid (i.e., B-30).

bridges (Figure 1).[1-2] The three dimensional structure of insulin has been elucidated by Dr. Dorothy Hodgkin and co-workers via x-ray crystallography, and with that type of analysis, insulin appears to be a globular protein containing an alpha helix, an antiparallel B pleated sheet, a hydrophobic interior, and a hydrophilic exterior.

The pronounced hormonal potency of insulin in many tissues results from its ability to regulate a wide variety of cellular processes.[1-3] The net result of insulin's actions is both to promote the storage and utilization of metabolic substrates, and to increase the synthesis of macromolecules. Insulin is capable of exerting these anabolic effects because it is able to influence cellular functions at a variety of subcellular levels. For instance, insulin increases transport at the cell membrane; activates or inhibits enzymes in the cytosol, mitochondria and endoplasmic reticulum; stimulates new protein synthesis in the rough endoplasmic reticulum, and regulates deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis in the cell nucleus (Table 1). The question that arises, however, is how can a small protein like insulin carry out such a wide variety of diverse effects in target tissues.

At present there are two theories of insulin action, as shown in Figure 2. The first theory, the second-messenger theory of insulin action,[1,4] is based by analogy on the action of hormones such as glucagon. Glucagon acts via a second messenger, cyclic adenosine monophosphate (cyclic AMP), that is generated at the plasma membrane and in turn carries out many, if not all, of the intracellular effects of glucagon. For a number of years, investigators have postulated that a similar type of second messenger exists for insulin. For instance, Ca^{+2} and cyclic guanosine monophosphate (cyclic GMP) have been considered as candidates for this role. At present, however, no unique second messenger for insulin has been discovered.[3] The other theory, favored in our laboratory, is the direct intracellular binding theory of insulin action.[3,5] This theory is based on two recent observations. The first is that specific binding sites for insulin are present not only on the plasma membrane of target cells, but also on intracellular organelles, such as nuclei, smooth and rough endoplasmic reticulum, and Golgi membranes.[3-5] The second observation is that insulin can enter target cells and bind to these sites.[5] Therefore, it is possible that insulin directly regulates functions at a variety of cellular levels and a second messenger is not needed. Further studies will be necessary to discern which of the two theories is the correct one.

Measurement of Hormone Receptors

The modern era of measuring hormone receptors began in 1970. Before this, investigators had employed radiolabeled hormones to measure hormone binding sites on target tissues, but these

TABLE 1.—*Actions of Insulin at Various Subcellular Levels*[1-3]

Cell membrane
Stimulation of transport: sugars, amino acids, fatty acids, ions and nucleic acid precursors
Activation and inhibition of enzymes
Change of membrane potential
Alterations of cell surface morphology
Cytosol
Activation and inhibition of enzymes
Endoplasmic reticulum
Activation and inhibition of enzymes
Ribosome
Increased protein synthesis
Mitochondria
Activation of enzymes
Lysosome
Inhibition of protein degradation
Nucleus
Modulation of DNA and RNA synthesis

studies were plagued with two problems. The first problem was whether radiolabeled hormones (usually one made radioactive by substituting one or more iodine atoms into tyrosine residues) were biologically active. The second was whether the binding observed represented the interaction of the hormone with a biologically important binding site, that is, a receptor. Both these problems were simultaneously overcome in the laboratory of Dr. Jesse Roth, who in collaboration with Dr. Robert Lefkowitz and others prepared biologically active iodinated adrenocorticotropic hormone (ACTH) and showed its binding to specific receptors in adrenal tissue.[6] Soon afterwards Dr. Roth, in collaboration with Dr. Pierre Freychet, carried out similar studies for insulin.[7] Subsequently, a large number of laboratories began to measure the binding of insulin to receptors in target tissues.

The methodology employed for measuring polypeptide hormone binding to receptors (radioreceptor assay) follows the same basic techniques as devised by Drs. Solomon Berson and Rosalyn Yalow for the radioimmunoassay of polypeptide hormones. In radioreceptor assays, hormones are first radiolabeled (usually either with iodine 125 or iodine 131) under conditions where the biological activity of the hormone is preserved. Next, either isolated whole cells or purified subcellular fractions are employed and the binding of the hormone to receptors is measured.

Radioreceptor Assay of Insulin

Currently, we are able to measure insulin receptors in a wide variety of tissues and cell fractions. In particular, isolated lymphocytes, fat cells

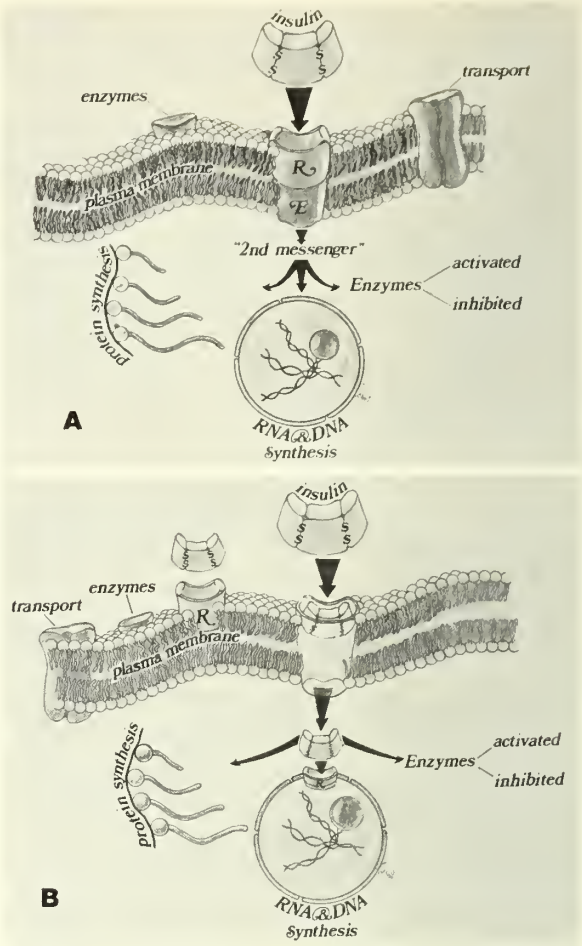

Figure 2.—Theories of insulin action. **A**, second messenger theory of insulin action. **B**, intracellular binding theory of insulin action.

and liver cells are commonly used. One interesting aspect of this line of research is that the insulin receptor is very similar in all tissues from a variety of species, and, therefore, a characteristic of an insulin receptor seen in one tissue usually applies to receptors on other tissues.[4-8] The insulin receptor appears to be a protein with four subunits and the entire molecule has a molecular weight of approximately 300,000 daltons.[2,4,8] This receptor has a high affinity for insulin (Kd 10^{-8} to 10^{-10}M) and specifically binds only biologically active insulins or insulin derivatives.[2,4,8] The most widely characterized subcellular fraction where insulin receptors have been studied is the plasma membrane (cell surface membrane) of a variety of isolated cells. In addition, we can measure specific insulin binding sites in smooth and rough endoplasmic reticulum, Golgi membranes and nuclear membranes.[3-5] Interestingly, the receptors

TABLE 2.—*States of Insulin Sensitivity and Resistance That Correlate with Receptor Defects*

	Receptors	*Plasma Insulin*
Sensitivity		
Hypophysectomy	Increased	Decreased
Adrenalectomy	Increased	Decreased
Resistance		
Obesity	Decreased	Increased
Glucocorticoid Excess	Decreased	Increased
Diabetes Mellitus:		
With Hyperinsulinemia	Decreased	Increased
With Acanthosis Nigricans	Decreased	Increased
With Lipodystrophy	Decreased	Increased

TABLE 3.—*States of Insulin Resistance That Suggest Postreceptor Defects*

	Receptors	*Plasma Insulin*
Growth Hormone Excess	Unchanged	Increased
Aging	Unchanged	Increased
Fasting	Increased	Decreased

TABLE 4.—*Decreased Binding of Insulin to Circulating Monocytes from Obese Humans**

	Percent Insulin Bound (10^8 cells /ml)
Thin Controls	6.0±1.1
Obese	2.8±0.3

In these studies monocytes were isolated from the blood of both normal thin controls and obese subjects. These cells were then incubated with radioiodinated insulin and the specific binding measured.

*Adapted from Roth, et al.[8]

on these intracellular organelles have certain binding characteristics that are similar to those found on plasma membranes.

States of Altered Sensitivity to Insulin

It is known that the sensitivity of target tissues to hormones, such as insulin, can be altered at several levels. These levels can be classified as prereceptor, receptor and postreceptor. A classic example of prereceptor insulin resistance is the case of an insulin-requiring diabetic patient who has very high circulating levels of anti-insulin antibodies. Soon after the ability to measure insulin receptors in target tissues became available, investigators then looked at the status of the insulin receptor in a variety of states of altered sensitivity to insulin to determine whether receptor or postreceptor changes exist (Tables 2 and 3). Today, I will primarily discuss states of altered sensitivity to insulin that result from alterations in the insulin receptor. Two well-known clinical states of insulin resistance associated with receptor

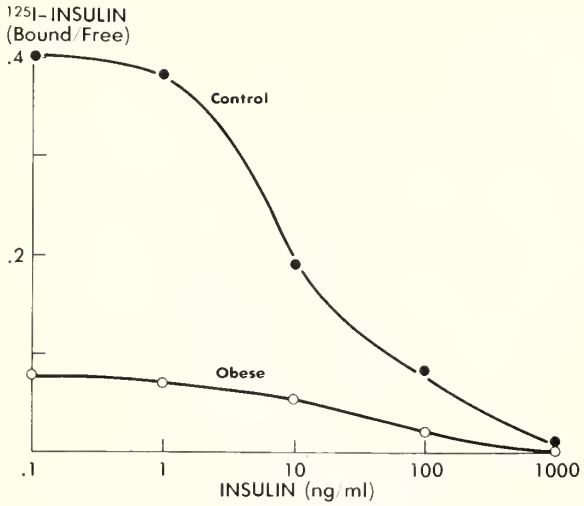

Figure 3.—Decreased binding of insulin to liver plasma membranes from obese hyperglycemic mice when compared with normal thin litter mates. For convenience, in these and subsequent figures, the radioreceptor binding data will be plotted in a manner similar to that commonly employed for radioimmunoassay; that is, the ratio of bound over free labeled insulin as a function of the logarithm of the insulin concentration in the binding reaction. This type of plot reflects both the affinity and capacity of the binding site. (Adapted from Kahn[4] and Roth, et al.[8])

changes are those associated with obesity and glucocorticoid excess. Two classic states of enhanced insulin sensitivity which appear to be related to receptor changes are those that occur following hypophysectomy and adrenalectomy. In addition, hyperinsulinemic diabetes is considered by some investigators to be an insulin resistant condition.

States of Receptor Alterations

The first state of insulin resistance to be investigated intensively was that of obesity. Initial studies were done with an animal model of pronounced obesity, obese hyperglycemic mice.[4,8] These are animals with a pair of recessive genes that cause massive obesity. They are hyperglycemic despite 10- to 100-fold elevations of plasma insulin levels. When plasma membranes from liver or fat are prepared from these animals, and compared with either normal animals or normal litter mates, the binding of insulin is notably diminished (Figure 3). If these obese animals are fasted to reduce body weight, plasma insulin levels decrease and the diminished binding tends to return to normal. The same features are seen in humans with acquired obesity (Table 4).[8] When insulin receptors on their circulating blood monocytes

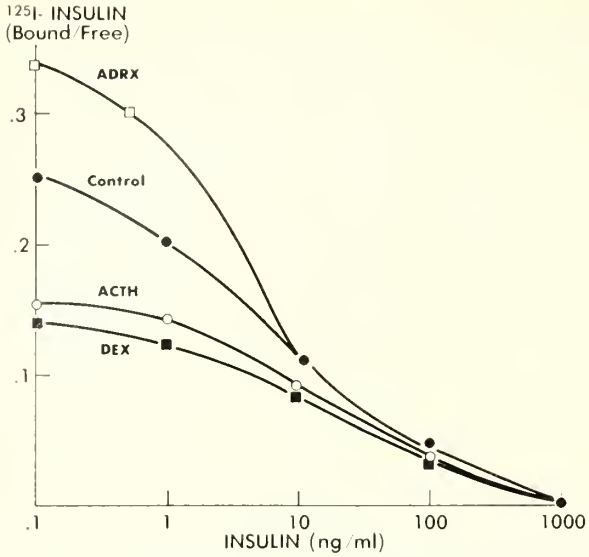

Figure 4.—Binding of insulin to liver plasma membranes from control, adrenalectomized (ADRX), adrenocorticotropic hormone (ACTH) treated and dexamethasone treated (DEX) rats. I. D. Goldfine and C. R. Kahn (unpublished observations).

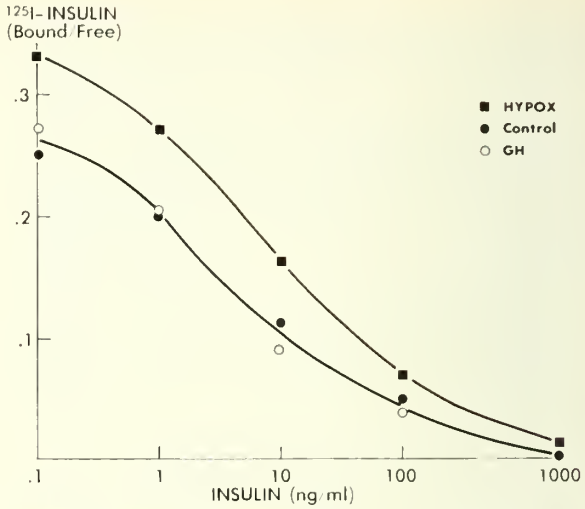

Figure 5.—Binding of insulin to liver plasma membranes from control, growth hormone treated (GH), and hypophysectomized rats (HYPOX). I. D. Goldfine and C. R. Kahn (unpublished observations).

are measured, it can be seen that cells from obese patients have a greatly diminished ability to bind insulin.

Another instance of severe insulin resistance is that which can occur during states of glucocorticoid excess. Although corticosteroids can rapidly antagonize certain effects of insulin—such as those effects on glucose transport—without influencing insulin receptors, it recently has been observed that either steroid or ACTH treatment of animals for several days is associated with a decrease in the binding of insulin to receptors in liver and fat (Figure 4). Therefore, chronic hyperglucocorticoidism is another clinical state of insulin resistance, where the insulin receptor appears to play a role in the development of this clinical problem.

There is a unique syndrome of extreme insulin resistance associated with acanthosis nigricans and various immunological problems.[9] In one group of these rare patients, a circulating antibody to the insulin receptor can be detected. This antibody competitively blocks the binding of insulin to target tissues, and it is believed that the presence of this antibody accounts for the insulin resistance observed. In lipodystrophy, there is insulin resistance, and it recently has been observed that patients with this problem have a diminished number of insulin binding sites on their circulating monocytes.[10]

We will next consider two insulin sensitive states, that following hypophysectomy and that following adrenalectomy. In both instances, plasma membranes from animals with these conditions bind more insulin than membranes from control animals (Figures 4 and 5). Consequently, it is possible that the increased number of receptors seen in these two states may account for their increased sensitivity to both endogenous and exogenous insulin.

Insulin Receptor Regulation by Insulin Itself

Before discussing the status of the insulin receptor in diabetes mellitus, I wish to mention important new data concerning the regulation of the insulin receptor by insulin itself. When certain insulin sensitive and insulin resistant states are examined, it becomes apparent that an inverse correlation exists between the insulin levels in the plasma and the number of insulin receptors in target cells (Table 2). Therefore, in certain states of insulin resistance where there are high insulin levels, such as obesity or glucocorticoid excess, the number of insulin receptors are decreased. Inversely, in certain states of insulin sensitivity, when insulin levels are decreased, such as after hypophysectomy or adrenalectomy, the number of receptors is increased. Drs. Jesse Roth and James Gavin, and their colleagues, undertook studies to determine if there is a direct correlation between these two factors.[8] To determine whether an effect of insulin was mediated directly

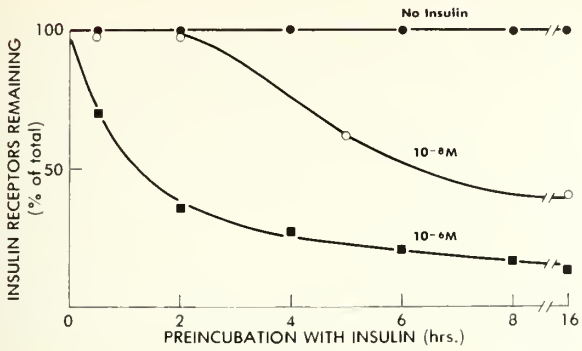

Figure 6.—*In vitro* demonstration that insulin itself can regulate its own receptor. (Adapted from Roth, et al.[8])

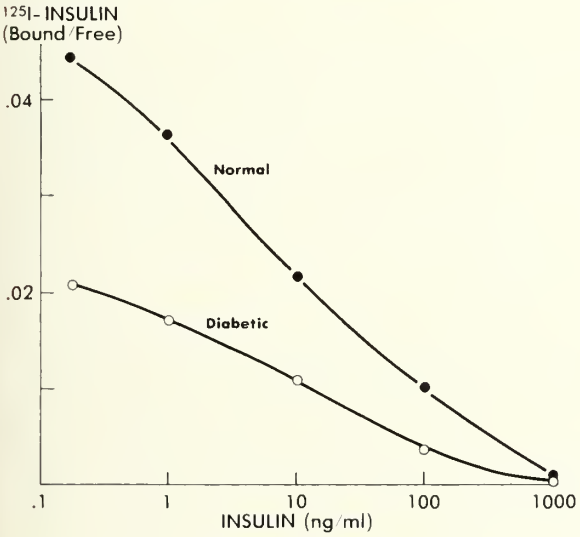

Figure 7.—Binding of insulin to monocytes from normal and diabetic subjects. (Adapted from Olefsky and Reaven.[11])

by insulin and not indirectly through changes in other hormones or metabolites, they employed an *in vitro* system, isolated human cultured lymphocytes. These cells, which are maintained in permanent culture, have large numbers of insulin receptors that are virtually identical to those seen on classical target tissues for insulin, such as liver and fat. When they preincubated these cells with unlabeled insulin for varying periods, and then extensively washed the cells to remove any insulin bound to the surface, they found that the subsequent binding of radiolabeled insulin was diminished (Figure 6). When they employed high concentrations of insulin, such as 10^{-6}M, they found that after periods as short as 30 minutes a significant fall in the insulin receptors could be detected. At this concentration, greater than 75 percent of the receptors were lost after

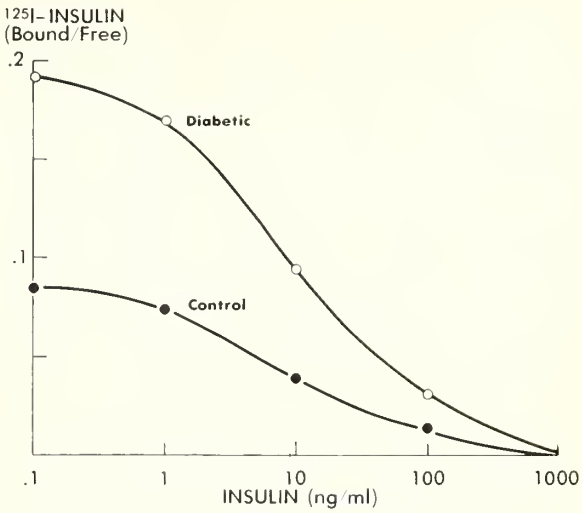

Figure 8.—Binding of insulin to liver plasma membranes from control and streptozotacin-diabetic rats. (Adapted from Davidson and Kaplan.[12])

eight hours of incubation. Similar effects, smaller in magnitude and slower in onset, were seen with more physiological concentrations of insulin,* 10^{-8}M. They postulated that insulin autoregulated its own receptor in an inverse fashion and then made the interpolation of these *in vitro* experiments to *in vivo* studies. It is now apparent that, *in vivo,* high concentrations of insulin will lower the number of insulin receptors on a number of target tissues. This observation provides a partial explanation for the changes in number of receptors noted in the aforementioned studies.

Insulin Receptors in Diabetes Mellitus

There has been a controversy for a number of years concerning whether insulin resistance exists in diabetes mellitus. There appear to be convincing data that in patients with mild to moderate diabetes who have higher than normal levels of insulin, there is insulin resistance. This subject has been extensively studied in the laboratories of Drs. Gerald Reaven and Jerrold Olefsky.[11] When the binding of insulin to circulating peripheral monocytes from such diabetic patients is examined, cells from these subjects bind approximately half as much insulin as do similar tissues from control subjects (Figure 7). In contrast, when animals with experimental diabetes are studied, a different picture comes forth. In diabetic animals studied by Drs. Mayer Davidson and Solomon Kaplan[12] there is an increase in the

*The basal fasting concentration of plasma insulin in man is approximately 10^{-10}M (0.6 ng/ml or 15 μU/ml). After stimulation this level can rise 10- to 100-fold.

TABLE 5.—*Plasma Insulin Levels and Glucose Values in Diabetic Humans and Rats*

	Glucose (mg/dl)	*Insulin (μU/ml)*
Humans[11]		
Controls	89±6	11±1
Diabetics	203±18	21±2
Rats[12]		
Controls	145±2	26±2
Diabetics	515±12	7±1

binding of insulin to target tissues when compared to controls (Figure 8). The apparent discrepancy between the findings in humans and those in animals can best be understood when the insulin levels in the patients and animals are examined (Table 5). In these diabetic humans the insulin levels are higher than normal and, therefore, in light of the previous data concerning autoregulation of insulin receptors it is not surprising that their receptor concentrations are diminished. In contrast, the insulin levels in the diabetic animals are decreased, and therefore, it is also not surprising that their receptor levels are increased. Therefore, it appears that in diabetes there can be either an increase or decrease in insulin receptors, depending on the plasma insulin level.

States of Postreceptor Alterations

There are several conditions in which the insulin receptor does not appear to play a major role in the altered response of target tissues to insulin and the altered responses, therefore, are subsequent to receptor binding. One such state is that of growth hormone excess or acromegaly. In certain studies, up to 25 percent of acromegalics have been found to be either diabetic or have notably abnormal glucose tolerance tests. When rats are injected with growth hormone, however, there is very little difference in the binding of insulin to plasma membranes despite elevated levels of plasma insulin (Figure 5). Therefore, states of growth hormone excess, in contrast to obesity and glucocorticoid excess, may not be associated with major alterations in the binding of insulin (Table 3).

Another condition associated with postreceptor alterations is fasting, where insulin receptors are increased but insulin resistance is present. A third postreceptor condition is aging, an insulin resistant state where receptors are unchanged in liver and lymphocytes, but where the response of these tissues to insulin is decreased.[13]

Future Directions

The studies I have discussed indicate that insulin receptors, and especially the receptors present on the plasma membrane of target cells, are altered in several states of either insulin sensitivity or insulin resistance. Although the metabolic changes that occur in these various states are complex, it would appear that changes in the insulin receptor in certain conditions contributes to the abnormalities observed. Many important questions, however, remain unanswered.

One question is how are the cell-surface receptors for insulin regulated by insulin itself. One possibility is that insulin influences target cells to decrease receptor synthesis. Another is that insulin may irreversibly alter the conformation of its receptor so that the receptor loses its binding capabilities. A third possibility, which I believe is the most intriguing, is that after binding to its cell surface receptor, both insulin and its receptor enter the cell together. The receptor could be degraded while insulin then binds to intracellular binding sites.

Since plasma membrane binding sites are altered by insulin, the question arises whether in the same conditions intracellular binding sites for insulin change in concert with those on the cell surface. Recent studies by Dr. Riccardo Vigneri and myself indicate that the intracellular binding sites on nuclei and on smooth and rough endoplasmic reticulum are also regulated by insulin itself in a manner very similar to that seen for those sites on the plasma membrane.

From a clinical point of view, the question arises as to the importance of the regulation of the insulin receptor by insulin itself during various treatment regimens. For instance, it has been noted that in the treatment of diabetic ketoacidosis, the administration of very small amounts of insulin can lower sugar and ketone levels in a manner comparable to that obtained when very large amounts of insulin are employed. On the basis of the aforementioned data, it is possible that by giving very large amounts of insulin there can be a rapid loss of insulin receptors induced by insulin itself. This process, in turn, would increase the need for more insulin, setting up a vicious cycle. It would seem that one of the potential benefits of using smaller amounts of insulin for treating diabetic ketoacidosis would be to avoid this phenomenon. Another similar clinical problem could occur in the chronic treat-

ment of patients with diabetes mellitus. It would appear possible that by administering excessive amounts of insulin, a reduction in the number of receptors would occur which, in turn, would continue the need for large doses of insulin.

It appears, therefore, that a new era in diabetes has opened with the ability to measure the insulin receptor in target tissues. These studies have been applied in various forms of primary and secondary diabetes and exciting new data have been obtained. I believe, therefore, that in the next few years much more data will come forth to help us understand the biochemical mechanisms underlying these conditions.

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The Surgeon Who is a Bacterial Shedder

If you knew you were a shedder, what would you do?

I would first decide where I was shedding, and there are a number of places where you can shed: you can shed from the skin (generally, that's few and far between); you can shed from the nasopharynx (that's, I think, the most common source of shedders); you can shed from axilla or the groin or you can shed from the perineum. People tend not to . . . shed in all places at once; they seem to shed from one place or another. And then you go to work on the area that's causing the trouble. Experience says that by using topical antibiotics aimed specifically at the bacteria that's causing the problem (and it's usually a staphylococcus aureus of one type or another), the sources of the bacterial growth on the surface can be controlled and the shedding eliminated. Now, this probably is going to be a recurrent problem, because you can wipe it out for a little while and then you are going to start regrowing it again, so I think the person who is a shedder has to be continually alert to the problem. But I think that it's not an impossibility. You don't have to go into dermatology or x-ray or some other fancy specialty. You can continue in surgery safely, I think, if you pay attention to the problem and deal with it sensibly.

—JOHN F. BURKE, MD, *Boston*

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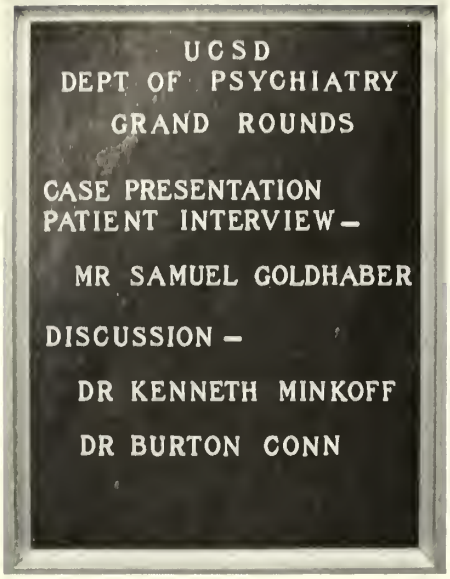

An Obsessive-Compulsive Neurotic Patient in Crisis

Based on Psychiatric Grand Rounds audiotaped at the Curtis W. Gifford Mental Health Clinic, a teaching facility of the School of Medicine, University of California, San Diego, in early 1976, edited by Barbara Wilkes Blomgren.

MR. GOLDHABER:* We are going to talk about a patient we will call Mary† this morning. She is a married white housewife in her middle 30's who asked to see a crisis service therapist during her husband's intake session at Gifford Clinic one day last fall. Her chief complaint was "I'm afraid of harming my children." Her husband complained that she was drinking alcohol heavily and could no longer care for the five of their seven children who were still living at home. The family had moved from Denver to a black neighborhood in San Diego two months before. The children were afraid to go to school or play outside. Mary had stopped eating and neglected her housework, no longer even preparing meals. She admitted to drinking up to 12 beers a day for the past two years and said that she liked drinking. She said that she had been on a binge for two weeks. A week earlier Mary had been admitted to a local hospital for an elective hysterectomy, but at the last moment she refused to sign the operation permit. She explained that she wanted to keep the option to have children, although she had had a tubal ligation nine years earlier. Her husband's explanation was that she did not want to go without alcohol. We assigned a diagnosis of habitual excessive drinking, and I saw Mary twice a week for five weeks; then we transferred her to the outpatient service at Gifford Clinic for longer-term therapy.

Mary was the fourth of eight children born to a middle class Midwestern Catholic family. She described her mother as a healthy, talkative woman, who never hit the children. The mother was a compulsive housekeeper who "cleaned out corners with a knife." Mary was breast-fed. She had no significant childhood illnesses, perinatal trauma or separation from her parents. She and her sisters were afraid of their father, who was very strict. Neither parent had a history of mental illness or alcoholism, but one sister has had a nervous breakdown. When asked for her earliest memories, Mary remembered "doing mean things." She bit a little girl who gave her a mean look (and was bitten by her mother as punishment). She was punished for breaking a car window. Her father did not like her brother. Her father was afraid that the children would drown in a nearby irrigation ditch. She was afraid of falling into the outhouse hole. Around the age of

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†The patient's name is fictitious.

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5 she tied a cat to a post and beat it to death with a stick, while her brother threw rocks at another cat.

Mary went to Catholic schools through high school and did well. As early as the age of 10 she had constant worries that blasphemous thoughts might injure her relationship with God. She also had fears of glass in her food at that time, and many compulsive rituals such as walking up and down the stairs a set number of times. Her confessions were so detailed that the priest begged her to cut them short. Her father threatened to take her to a hospital to get her to control her symptoms. She began dating late in high school and married her present husband one month after graduation, following a 15-month courtship. He was the first boy she dated, and the only one with whom she had had sexual intercourse. She stopped practicing Catholicism at age 27.

Mary has seven children, aged 18, 17, 16, 14 and 9, and twins who are 12. The oldest two children are out of the home, and all of them are doing well. Except for her persistent obsessional fears Mary was able to function as a housewife and mother until shortly after the birth of her fourth child, in 1961. She became unable to care for her child because of a strong fear of killing him. The fear of poisoning from germs also incapacitated her. She was admitted to hospital for five weeks at Colorado State Hospital and was discharged improved. Two years later she again was admitted to hospital with similar symptoms shortly after the birth of her twins. She began a day hospital care program six weeks after the birth of her seventh and last child; then she was treated as an inpatient for three weeks. At that time she was described in the record as chronically afraid that pieces of glass were getting into her washing and might kill someone. She described many problems of trying to dress herself; sometimes it took two hours because she was afraid that something was wrong with her clothes. She also expressed fears of getting glass into food; at times she found it difficult to cook meals because of these feelings. During that hospital stay she was treated with chlorpromazine (150 mg per day) and trifluoperazine (10 mg per day).

Since 1966 at various times she had short-term psychotherapy, day treatment and therapy with psychotropic medicine including chlorpromazine and trifluoperazine. According to her history she has responded to all modes of therapeutic intervention and between episodes of decompensation she has functioned as a wife and mother and has been employed as a barber. Eight months ago she stopped taking the antidepressant doxepin hydrochloride, and apparently she did well until the family moved to San Diego.

At the intake interview Mary was dressed sloppily. Her breath smelled of alcohol, and her speech was slurred. She staggered slightly as she walked. At times she had difficulty concentrating and left ideas and sentences unfinished. Her affect was childlike and labile. She would cry, and then several minutes later seem inattentive and far removed from the interview. She said she had no idea why she was afraid of harming her children. She stated emphatically that she loved them. She was oriented to person, place and time. Her insight and judgment were poor. I recommended strongly to her that she receive detoxification treatment. She refused adamantly, but two days later she telephoned me and said she had changed her mind.

I arranged for her immediate admission to the Women's Detoxification Center, where she stayed for three days. At our next Gifford session we identified her major problems as (1) the distress and incapacity that her obsessions were causing her, (2) serious marital difficulties, (3) fears of large groups of people and (4) fear of fear itself. Her main obsessions were fear of harming her children, of poisoning her family with moth flakes in the sugar bowl, of poisoning them with hookworm from hamburger meat and of accidentally swallowing glass chips. Her affect continued to be anxious and depressed. She had difficulty falling asleep and remaining asleep. She felt her life was worth very little, but she denied suicidal ideas. Her symptoms were not alleviated with administration of diazepam (10 mg twice a day), so amitriptyline hydrochloride was prescribed, and a maintenance dose of 200 mg per day (taken before bedtime) was reached in four days.

Less than a week later Mary's husband suddenly started screaming that *he* wanted to kill the children. He went to a kitchen drawer to get a knife, but Mary stopped him. They then rented a room near the beach for a week to provide him with a place to cool off. He later apologized to his children, and they decided to move the family into an apartment near the beach. Mary began feeling better a week to ten days after beginning to take the tricyclic antidepressant medicine. Her obsessions bothered her less and less. She and her husband became active in Alcoholics Anony-

mous and acquired sponsors. She has not had alcohol since she left the detoxification center. She has started to sleep and to eat well. At our termination session we discussed her hysterectomy, which had been rescheduled for two weeks hence, and the possibility of her returning to barbering part-time. When she was transferred from the crisis service to the outpatient department we added obsessive-compulsive neurosis and primary unipolar depression to the diagnosis of habitual excessive drinking. Now we will show a segment of the interview we videotaped the day Mary began taking tricyclic medicine.

Mary: I'm still not convinced I'm an alcoholic. I went to that meeting again last night. Not that I'm ashamed to be going. I feel like I'm not any better than those people. I feel like I'm not better than anybody else. I remember last week when I was telling you about that problem about nigger town. I don't mean to call them niggers and run them down. I don't mean it that way. It's just an old expression to call them niggers. Now you're supposed to call them blacks. Well, I like black people. I'm not prejudiced, you know. I know black people and I meet them out there at AA, and I like them and everything, and I want to go and keep going to them, but it still doesn't solve all the problems, you know.

MR. GOLDHABER: No. No one said it would solve all the problems. Why don't you tell me more about the other problems.

Mary: Well, they're still there yet. The thing I told you about—it's probably hard for you to remember—that business about the meat. Well, that night I got to thinking maybe we could still eat that meat, but maybe it'd be too late. The next day I rinsed the jug out real good, you know, and then I thought about that meat jug again today.

MR. GOLDHABER: How could you have more problems with that today?

Mary: That was last night. Last night I had this frozen package of hamburger. I was in a hurry to put more ice in that jug because everybody likes ice water. But the hamburger was in there thawing for supper, so I took the hamburger out and right away took the jug and dumped them [pieces of ice] in there from the ice thing. And then I got to thinking, well, my hands were on that meat thing, and I didn't wash my hands before I touched the water and dumped them in there, and then I thought maybe there were still some of those germs in the water jug.

MR. GOLDHABER: Wasn't the meat wrapped?

Mary: Yeah, but still sometimes when that stuff sticks around . . .

MR. GOLDHABER: You mean from the defrosting? Some of the blood? You were afraid that was going to contaminate the ice water pitcher?

Mary: Yeah. But I did leave the water in there. But still in my mind I didn't know whether I should have dumped all that water out or not. But I did leave it in there again.

MR. GOLDHABER: Now you're worried you're going to poison your whole family with hookworm?

Mary: Yeah. I'm still taking that chance. Like I did the last time. I took ten chances with that already. And then, well . . .

MR. GOLDHABER: Wait a second. Let's talk about the hookworm for a minute, OK?

Mary: OK. That really is a bother to me.

MR. GOLDHABER: Do you think that the fear of hookworm poisoning is realistic?

Mary: To me it seems so much realistic that I worry about it. I know this meat is supposed to be government inspected, but I don't really trust things like that.

MR. GOLDHABER: They don't inspect every cow, that's for sure. They only do spot checks.

Mary: I figure this has got to be a germ, and you can't see a germ. Maybe if it's an egg maybe I could feel it with my finger. But I don't know about the hookworm, if it's transferred through a germ or what. And what's when I'm all worried about meat. I don't care whether it's chicken or what it is. Of course then when I stop and think at that extreme, doesn't it mean that the hookworm could be on the cereal box? It could be on anything I touch, and I can't go wiping that all off. Then I get to thinking I can't go to them extremes—I'd never never be able to do all that stuff.

MR. GOLDHABER: To you it's a very realistic fear Tell me, have you ever known anyone who has had hookworm?

Mary: Never did. Never have known anybody that had the hookworm.

MR. GOLDHABER: Of all things to be afraid of, why do you think that's one of the things you're particularly scared of?

Mary: Because I think I've heard that once you get that hookworm, that's it. There's no cure. You just die. That worm just keeps growing or something and hooks in your throat or something and then you die. I never worry about myself dying. I'm really not . . .

MR. GOLDHABER: You're thinking about your kids and . . .

Mary: Anybody else. I'm not afraid to eat it myself, but if I did, well, don't let any of the others eat it, you know. And sometimes it kinda looks bad in the refrigerator. I'll first taste it and see if it's good. I always have done that. And if it's poison, well, if I die, that isn't that much, you know. I just don't wanta hurt somebody else.

MR. GOLDHABER: If you die, that's not much? What do you mean by that?

Mary: I don't know. That's the way I feel.

MR. GOLDHABER: Why do you feel that way?

Mary: I feel that that wouldn't be a . . . be a . . . it would be a terrible crime to hurt somebody else.

MR. GOLDHABER: Why do you feel your own life is worth so little?

Mary: Well I don't want to waste the food either, and I don't figure my own life is worth as much as theirs is. I don't know. But sometimes you gotta taste something to know if it's spoiled yet, don't ya? A little taste sure ain't gonna kill me.

QUESTION FROM THE AUDIENCE: *Were her attitudes toward the hysterectomy looked into?*

MR. GOLDHABER: Her attitude toward hysterectomy per se, no. Her attitude toward tubal ligation, yes. Originally a priest had counseled her that it would be all right for her to have a tubal ligation at the time she gave birth to her seventh child. Another priest told her afterward that she had sinned and she would really need to try to reverse the operation. She had a lot of guilty thoughts about it.

QUESTION: *When this tape was made, how long had she been off alcohol?*

MR. GOLDHABER: About two weeks, and she was just starting on the tricyclic that night.

QUESTION: *What did she say the alcohol did for her?*

DR. MINKOFF:* My understanding was that she felt it helped her to deal with her obsessions and some of the anxiety surrounding them. Also, her husband is an alcoholic, and it may have been a way for her to participate in what was going on in the household.

QUESTION: *What was the evidence for unipolar depression as opposed to depressive neurosis or something like that? On the tape she seemed a little depressed, but not a lot.*

MR. GOLDHABER: I based it mainly on her history. She had become functionally inadequate on three occasions, right after the birth of her children; she had to be admitted to hospital. That suggested primary affective disorder or unipolar depression to me. I think she was getting slightly better by this interview. One point Dr. Minkoff made as we reviewed the tape was that she seemed to be able to relax somewhat by means of her obsessions. They provided a pleasurable outlet for her. We turned the sound off and watched her just sitting back there and gesticulating and relaxing, and it seemed that she was getting some enjoyment from it.

DR. MINKOFF: Although Mary wasn't given formal psychological testing at Gifford Clinic, for similar episodes in the past she had had testing and the results supported a diagnosis of obsessive-compulsive neurosis and some postpartum depression. She doesn't appear to have looseness of association or other criteria for a diagnosis of thought disorder, such as thought broadcasting, or ideas of influence, control or reference, or hallucinations. And her course over a long period does not suggest the course of someone with thought disorder. Except for this episode, all the distinct exacerbations of her problems occurred postpartum. Although she had obsessions in the interims, they were not as severe and debilitating as those you saw here, and they had even less quality of thought disorder.

I feel this patient is one to whom different models of psychiatry can be applied very well. I am going to use a crisis model in describing her intake and the way we dealt with her initially, and then Dr. Conn will talk about her from the psychodynamic standpoint. Her symptoms are so clear-cut that it is easier to distinguish between baseline and exacerbation than it might be in the

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behavior of someone with a more ordinary personality problem.

In a crisis model, as Gerald Caplan[1] describes it, a person exists in a baseline state preceding the occurrence of some kind of stress or hazardous event. Everyone has an individual repertoire of coping mechanisms for everyday use. When the hazard or stress appears, he will use his usual coping strategies to get back in equilibrium. If his usual strategies succeed his behavior will gradually return to baseline, and you won't notice anything bizarre or very unusual. For example, this morning I woke up an hour early and found myself obsessively thinking about what I would talk about today; those are my usual techniques for coping with this kind of hazard. If they did not work there would be an increase of anxiety, an increase of feelings of helplessness, and an increase in disorganization and decompensation, and I might resort to unusual means to try to cope, something out of the ordinary pattern of my behavior.

In Mary's case there is a history of obsessive-compulsive neurosis dating back to childhood. Although the severity of her obsessions waxed and waned at different points in her life, it is likely that she has never been entirely free of them. Therefore, for the purposes of this discussion, this neurotic level of functioning can be considered her baseline. Her neurotic symptoms developed in childhood as efforts to cope with conflicts between sexual or aggressive impulses and a punitive superego. At best, though persistent, they have not interfered with her function as a wife, a mother and a barber.

However, look at what happens when she is under stress. A major stress that was not mentioned in the initial presentation occurred two years before we saw her: her husband became disabled, and she had to go to work to support the family. That stress probably exacerbated her obsessive symptoms, which constituted her usual method of coping. When the compulsive behavior did not work, she resorted to an "unusual" (for her) coping method, namely the use of alcohol. While not very adaptive, this enabled her to maintain equilbrium until the onset of a new stress—the move to a black neighborhood in San Diego two months before we saw her—which disrupted her already shaky equilibrium, and she increased her drinking in an effort to cope. But the increase in her *now usual* coping effort failed, and her behavior deteriorated. Finally a third stress—the impending operation—added to the already mounting crisis, and she came for help. The crisis in Mary's case was characterized by depression, anxiety, intoxication and failure to perform her roles.

The crisis model, therefore, provides a format for organizing Mary's recent experience and in so doing provides the basis for a treatment plan. The keynote of crisis intervention is the replacement of maladaptive coping behaviors with more effective new skills for dealing with the crisis-invoked feelings, enabling the patient to return at least to baseline. In Mary's case the first target was her drinking, which, although an effort to cope, was too severe to allow any other, more adequate, mode of coping. Her drinking was dealt with through confrontation and support, with a referral to AA as a more adaptive strategy for her to use in dealing with her anxiety. Without the disruptive influence of alcohol, and with the addition of more adaptive activities, she improved. However, she returned to an *intensified* level of her original style—the obsessive compulsions—as a means of dealing with persistent marital and environmental stresses.

These intensified obsessions were the next target symptoms. In crisis intervention the goal would not be to remove them, but to return her to a state in which her baseline neurosis interfered less drastically with her daily living. This was accomplished by prescribing antidepressant medicine and encouraging her to make positive moves to ease her living situation and improve her marriage. After six weeks of treatment she was regarded as back to baseline and was referred for longer-term treatment and consideration of modifying her baseline neurotic state.

I want to add that our apparently successful use of a tricyclic antidepressant in ameliorating her obsessive ruminations, the similarity of obsessive ruminations to the ruminations of depressive illness, and the association of her symptoms in the past with the postpartum period suggest that her exacerbated obsessive symptoms may represent a depressive equivalent over and above her baseline neurosis. Although she clearly lacks other evidence of depression, these factors do indicate that internal biologic stresses may have an influence on crisis states.

DR. CONN:* This very interesting case reminds me a little of the opening scene of "Mission Im-

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possible"—"Good Morning, Dr. Goldhaber. Your mission, should you decide to take it, is to try to convince Mary by logical reasoning that she no longer need believe in or be anxious about her compulsive rituals and obsessive ruminations. You have the rest of her anticipated life span in which to accomplish this."

The crisis model that Dr. Minkoff sketched is helpful in describing what happens, but it does not explain why. What I have to say in discussing Mary's difficulties is hypothetical. The only way to know whether hypotheses are correct is to have them confirmed by the patient during insight oriented psychotherapy or psychoanalysis. Nevertheless, I would like to use this crisis model in offering some hypotheses to explain what is going on.

I have to ask, why would moving, or her husband becoming disabled, or the birth of a child have this decompensating effect on Mary? Mr. Goldhaber's suggestion of biological predisposition to depression is tempting, but the usual depressive symptoms are not here, and there is very little in her history to suggest the vegetative signs and symptoms we ordinarily associate with endogenous depression. Moreover, I do not see how a move to San Diego or her husband losing his job could be interpreted as a biological stress.

I would like to suggest a reason the move to a particular area may have been a precipitating stress for Mary, a possible symbolic meaning for her of being admitted to a hospital briefly, and another possible reason the tricyclic drug therapy is apparently helping her. I will indicate what occurred to me as the case was presented, and that may show the kinds of ideas I get when I hear a patient giving such a history.

First, why does she ask to be seen in the crisis unit while her husband is having an intake interview there? He's come in apparently because of a problem with alcohol, and she becomes the focus of attention by voicing an obsessional idea that creates anxiety in her and certainly in the community of which we are a responding part, namely: "I'm afraid of harming my children." She presents us with a symptom that says she is afraid of losing control; the loss of control may involve aggression, and the aggression may be directed toward her children. She's asking people who are recognized as helpers in these kinds of things for help in controlling herself.

I would like to talk about the stress of moving to the black neighborhood. Here is a woman who comes in and says she is afraid of losing control of what is inside her. Apparently she has moved from one environment to another, and the new environment is full of hazards, people with uncontrolled aggression. This is my hypothesis: She moved to a place where there was a lot of aggression directed against her children; perhaps she felt it directed toward herself as well, and she felt she had less control over her external environment. One way to cope when you feel lack of control inside is to try to control your environment. For a woman already threatened by loss of control, moving into a neighborhood where she feels decreased control over her external environment might result in an increase in anxiety and an increase in her fear of losing control of what is inside.

The other precipitating factor, as I see it, was her admission for elective hysterectomy, when she refused to sign the operation permission. She wanted to have the option to have children. I wonder what it means to her to have this hysterectomy. Could the possibility of getting pregnant act, symbolically of course since she's had a tubal ligation, as some control over her sexual feelings and sexual behavior? If she did have the hysterectomy might she then be free to have sex in an uncontrolled fashion, something that she might find very threatening? That is one part of the picture. Another might have to do with the idea that a hysterectomy would in a sense kill her unborn children; that may have something to do with her aggressive wishes against her living children.

Her father was strict and frightening; apparently concerned about his daughters not being able to control their sexual feelings, he forbade Mary or her sisters to date until they were 18. Her mother was healthy—I do not know if that means psychologically or physically. She is also described as a talkative woman, and frequently people who are anxious talk a lot to control their anxiety. The mother was an obsessive-compulsive person in her own right, perhaps not an obsessional neurotic, but at least a compulsive personality, cleaning out corners with a knife.

Although it is interesting that Mary was breastfed and had no significant childhood illnesses, perinatal trauma or separations from her parents, we know nothing at all about her toilet training—at what age she was trained, what the stresses were, how the mother handled this—this would

be important information to have about an obsessional neurotic.[2]

Her earliest memories have to do with aggression and retaliation. She recalls doing mean things like biting a little girl who gave her a mean look. For that her mother bit her, reinforcing something that children believe in anyway—an eye for an eye. She remembers being punished for breaking a car window. Her father's fear of loss of control is reflected by his obsessional concern that the children might drown in the ditch; and then Mary developed a phobia about falling into the outhouse hole. She remembers losing control when she was about five years old and beating a cat to death. That was around the time her youngest siblings were born.

The strictness and rigidity of certain kinds of parochial education feed right into the absolute black-or-white, right-or-wrong thinking of children who already have problems with archaic, overdeveloped, and sadistic superegos or consciences. It has been classically stated from the psychoanalytic point of view that the obsessive-compulsive neuroses of childhood develop in latency, whereas the hysterias develop during the earlier Oedipal period, because the superego plays a strong part in obsessional neuroses, and the superego is not consolidated before the end of the Oedipal period.[2] This patient apparently decompensated under the stress of adolescence; her neurosis was not stable, not functioning effectively to control the amount of anxiety that she was feeling. The fact that the priest had to ask her to cut her confessions short brings to mind that the defense against a symptom can become an expression of the symptom. In a sense, she attacked the priest and her family with her intense and disrupting symptoms.

Although we know that she began dating late in high school and married her present husband after graduation, we do not know anything about her sex life or what she feels her sexual adjustment is.

Mr. Goldhaber: She and her husband have sex with each other and different partners, but they agree they always tell each other about it. She says sex in general is no problem.

Dr. Conn: That is a typical answer from an obsessional neurotic person when you ask about sex life. There is no problem there because the anxiety about sexual issues is being displaced into other things. Like climbing up and down the stairs thirty times a day. Or washing one's hands all the time. Or being afraid to touch the meat. Or a fear of hookworm infestation.

Now, I wonder why the first overt decompensation in adult life developed after the birth of her fourth child. Why after *that* birth? Why was that the worst one? My contention is that she has the information to explain that, and that it is potentially elicitable from her. Possibly, being a fourth child herself, she identified with that baby, and yes, she feels badly about herself. But she is in a hospital, she has the same old obsessional thoughts—poisoning, ground glass—she gets better. She has another child, she is admitted to hospital, she gets better after a few weeks. And so on. A typical symptom is that it takes her several hours to get dressed in the mornings. It has been suggested that such extended morning rituals may be to prevent masturbatory activity. No one is around, and there is an opportunity for autoerotic activity. The same has been said about some late night rituals.

I would agree with only part of what Mr. Goldhaber said about Mary's responding to all modes of therapeutic intervention, in the sense that for a brief time she recompensates to the baseline, but I wonder how much of her daily activity is affected by her obsessive rumination about dirt and guilt and bad things happening. How much of an effect is that having on her children and her relationships with them?

When Mary was in the hospital she received only about 150 mg of chlorpromazine and 10 mg of trifluorperazine a day. My feeling is that the brief hospital stays supplied something more important than the medicine: the control she feels she is lacking inside. In the hospital she does not have to worry as much about losing control over her internal impulses because she knows that there are external controls present. When obsessional neurotics have acute exacerbations of their neuroses they become fearful of losing control, and they generally get better with brief hospital stays because these provide relief from some of that fear.

So, some days after Mary starts to get better, her husband decides to have a crisis, maybe out of competitive feelings. After all, *he* is the one who came for intake in the first place. He starts screaming that *he* wants to kill the children now. Then they both get involved in AA. People with unmet dependency needs do very well in AA; they need not be true alcoholics. With a sponsor there's always someone to go to for dependency

gratification, and, particularly important for an obsessional neurotic, for some external control. There is a set of rules about how to act. Anytime you feel a weakening of your internal controls you can pick up the phone and call your sponsor, who will come over and stay with you. That's a made-to-order situation for somebody who is terribly afraid of losing control.

The fact that Mary has worked as a barber is of more than passing interest to me—she cuts it off, and then it grows back, and she does not have to feel guilty about it; she is forgiven for her wishes of castration; she is reassured that she has not committed any great wrong. This has to do with the basic psychoanalytic concept that obsessional neurotics are dealing with Oedipal conflicts although they regress to fixations at the anal level. A little girl wants to get rid of mother; she wants to have her father; she wants to have her father's penis—or what comes from her father's penis, which is father's baby—and she is fearful of retaliation from mother for her wishes.

I was struck by Mary's comment during the videotaped interview. "A little taste sure ain't gonna kill me." The thing that struck me was the isolation of her affect. She is not a depressive patient who is hurting, who is anguished. She sits there very relaxed with Sam, talking with smiles on her face about all these terrible things that she cannot get rid of while he is trying to reason her out of them. In fact, there is nothing now to suggest that Mary's mood was significantly depressed. My feeling is that she is not suffering from biological depression and does not have a unipolar affect disturbance. The sedating effect of the amitriptyline may well be helping her handle some of the mounting anxiety that the alcohol was handling before. If we substituted something else, either a minor tranquilizer in larger doses or a major tranquilizer in small doses, we might get the same effect, particularly if she took it at bedtime.

What *can* you do about the obsessions? I think one thing you *cannot* do is try to reason a patient out of obviously irrational ideas. She herself may say the ideas are irrational, but she still believes them. We have to recognize that these are symptoms, and we can approach them in one of two ways. We can deal with the symptoms themselves, the external behavior, with behavior modification techniques, through crisis intervention, with more external support and control (as she was getting here) and return her to baseline without affecting the underlying psychopathology. Or, if we feel she meets the criteria and if there is an analytically oriented or trained therapist available, she can be engaged in depth psychotherapy or psychoanalysis. Obsessive-compulsive neurosis is an indication for psychoanalysis.

DR. GRANT:* I do not believe any particular technique of psychotherapy is necessarily precluded by the crisis model, or that crisis intervention requires that specific techniques be used. Rather, crisis intervention should be thought of in terms of goals, and the goal here was to return Mary to her baseline level of functioning. Given the goal, several different strategies could have been used. There are books on psychodynamically oriented crisis intervention techniques.[3] One could also use cognitive approaches, rational emotive approaches and behavior modification. I think a number of therapeutic styles can fit the crisis model,[4] and that selection of strategies should be based on the expertise of the particular therapist and the patient's ability to relate to a specific approach.

DR. NEMIROFF:† The question came up about what to do therapeutically with her obsessions. I would like to mention one particular style that I have found useful in working with such a patient after getting to know her and developing a relationship with her. I tell her, "When I find myself worrying a great deal—worrying, worrying, worrying—I ask myself what I'm angry about. What am I resenting?" When you have a relationship with a patient you can put it to her just that way. You do not need to discuss the diagnostic specifics of hookworm, you try to get at the underlying aggression and resentment.

DR. JANOWSKY:‡ I agree that this patient does not have a primary depression. You might say that this excessive compulsive ritual is a defense against running amok or a defense against anything. I think she probably suffers from obsessive-compulsive neurosis. Klein and Davis[5] write about using amitriptyline to treat phobic anxiety states. Maybe that is a depressive equivalent, but another possibility is that it works for things other than depression, like premenstrual tension, that favorite entity, and postpartum problems.

I would worry when she first appeared whether this woman should be in a ward or not. I have

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seen people kill their kids after saying they are worried about killing their kids. If that is what she said (as opposed to worrying about their eating hookworm) I would have given serious thought to putting her in a hospital, and I am sure you did.

I agree too that it was not just the medicine that helped her, if that helped; I think it was the AA support and your support, Sam. Your interactions with her were very matter-of-fact: "What do you mean, hookworm?" You were telling her, "I care. I'm sort of a father for you. You're acting silly, little girl," in a positive, not a derisive way, and she was able to borrow your thinking.

The synthesis of the psychodynamic and the Caplan crisis model is an excellent way of looking at this case, it seems to me. It feels right to try to understand the dynamics *and* use a crisis, coping model of functioning as a basis for beginning treatment.

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Counseling a Patient with Cancer

DR. BURCHELL: "I think the crucial question which is seldom talked about but is on every cancer patient's mind is 'Will I be cured or will I die?' Most of us, as adults, when we approach our own death, tend to use the words, 'If I die,' or 'If I'm in an accident and die.' This is really a fallacious point of view because as a matter of fact all of us are going to die sometime. It would be more accurate for us to say, 'When I die,' but we seldom do this. I have found that a number of patients with cancer, after the diagnosis is made, shift subtly in their minds from an 'if' to a 'when' perspective. This may change back if they are quite sure they are cured. But this is a small change in words and a large change in concept, and has certainly major implications for the patients. The question of death has all sorts of complications for living. Some areas that particularly come to mind are commitments. Shall I commit myself to a new job? Shall I commit myself to investments? Shall I commit myself to long-term things in life? What about future planning?

"Any number of questions that come up for a normal person and are coped with quite easily, cause difficulty when raised with a patient with carcinoma—any patient with carcinoma, man or woman. They immediately focus on, 'What if I am not here two years from now?', so that there are many complications for living. Patients have taught me that the real horror in carcinoma is the horror of not knowing whether one is going to live or die. I think it helps very much in counseling patients to label this as a real problem, as perhaps the worst problem involved with carcinoma, and point out that there is really no solution until time gives the answer. It is very helpful, however, for patients to know that 'not knowing' is a major problem, that everybody feels this way and that they're not alone. I think I should emphasize . . . that I have been considering here patients who have just discovered they have cancer, and not those who are terminally ill."

—R. CLAY BURCHELL, MD, *Hartford, CN*

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Important Advances in Clinical Medicine

Epitomes of Progress — Neurology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in neurology. Each item, in judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in neurology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Neurology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Brachial Plexus Neuropathy

BRACHIAL PLEXUS NEUROPATHY may occur with or without a genetic basis. The clinical features of the hereditary neuropathy are indistinguishable from those in the spontaneous type, with one exception: in the former the onset is usually in the second decade or early third decade of life and patients have two to four attacks, while in the latter the onset is evenly distributed from the third to the seventh decade and recurrent attacks are rare. The disorder has been reported to follow immunizations, including influenza vaccine administration. Brachial plexus neuropathy is a rare disorder and is commonly misdiagnosed.

The onset is rapid, with constant rather than intermittent pain—usually in the shoulder, but also in the area of the scapula, arm, forearm and, rarely, the hand. In most instances muscle weakness develops rapidly within a few days to at most a few weeks after the onset of pain. Typically the pain lasts from several days to a few weeks and then gradually subsides. Muscle weakness is present in brachial plexus neuropathy but not in subacromial bursitis or bicipital tenosynovitis; conditions with which this neuropathy is frequently confused. Other diseases that should be considered in the differential diagnosis include cervical root disease, anterior horn cell disease and spinal cord tumors. In at least half of the patients the weakness is confined to the shoulder girdle muscles (deltoid, supraspinatus, infraspinatus). Involvement of peripheral nerves such as the radial or long thoracic nerve occur. Significant muscle atrophy is present in three quarters of all patients. In a few patients either unilateral or bilateral diaphragmatic paralysis is seen. Sensory loss occurs in two thirds of patients but may not be in the same distribution as the motor deficit. Two thirds of patients have unilateral involvement and one third bilateral involvement. The upper plexus is more frequently involved than the lower plexus. Laboratory studies including cervical x-ray films, lumbar puncture and myelograms are noncontributory. Occasionally the protein content of the cerebrospinal fluid is increased. Nerve conduction studies and electromyography will show abnormalities in those nerves and muscles that are involved. Only rarely is slowing of conduction observed elsewhere. In most patients improvement begins within the first few weeks of the onset of weakness, at which time the pain usually subsides.

Progressive neurologic disease related to the brachial neuropathy does not develop. Recovery in patients with upper plexus involvement is more rapid than in patients with lower plexus involvement. A third of patients will have recovered at the end of the first year, two thirds by the end of the second year and approximately 90 percent by the end of the third year. Residual weakness is usually in shoulder girdle muscles. No specific therapy is available and use of steroids does not appear to be of benefit. Pain relief during the acute phase and physical therapy for rehabilitation of patients are useful.

The diagnosis of brachial plexus neuropathy can be made readily in patients who present with the typical pattern of acute pain in or around the shoulder followed by weakness and without other symptoms or signs indicative of root or spinal cord disease. When the onset is in the first two decades and if there is evidence of recurrent attacks, the genetic form of this neuropathy probably is present. The long-term prognosis is good and supportive therapy is sufficient.

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Treatment of Asymptomatic Carotid Bruit

ALTHOUGH it is not common practice, some physicians use angiography in all patients with carotid bruits and, if a surgically correctable lesion is found, carry out carotid endarterectomy. Javid and co-workers have reported on the outcome in 56 patients with asymptomatic carotid bruits in whom endarterectomy was done. One patient died during the operation, postoperative strokes developed in two and strokes months after the operation developed in two. However, none of the 15 patients who died during an average follow-up of 36 months died from stroke. Twelve died from acute myocardial infarctions, one from gastric hemorrhage, one from liver failure and one from suicide. Thompson and Patman compared the long-term outcome in 49 patients with asymptomatic carotid bruits who were operated on with 59 patients who were not. In four of the patients in the operated group strokes developed immediately following operation or months later. In the nonoperated group, strokes developed in 14 patients. Unfortunately, the experimental group and the control group were distinctly different and comparisons between the two are of doubtful value. The likelihood of the patient with an asymptomatic carotid bruit developing a stroke has not been adequately assessed. Recently, Fields and Lemak reported that only 15 percent of 79 patients with transient ischemic attacks in the internal carotid perfusion territory suffered from strokes causing disability or death.

In an asymptomatic patient with a carotid bruit (regardless of its hemodynamic significance) but with cholesterol emboli in the fundus, angiography should be done. Angiography should also be done in patients in whom unequivocal abnormalities are found on Doppler ultrasonography, ocular plethysmography and ophthalmodynamometry indicating decreased internal carotid blood flow. During an angiography the intracranial vasculature always must be visualized. Whether or not further studies should be done in other patients who do not fulfill the above criteria is uncertain. The morbidity and mortality associated with carotid endarterectomy should be weighted against the low but significant risk of cerebral infarction without operation. Today an acceptable surgical mortality for carotid endarterectomy is 1 percent or less.

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Use of Anticoagulants in the Treatment of Stroke

BEFORE CARRYING OUT anticoagulation in a patient with stroke, one must decide whether the stroke is due to ischemia or hemorrhage. The distinction can be made easily when a patient presents with the usual clinical signs of subarachnoid hemorrhage, which are severe headache and stiff

neck. However, these findings are not present in many patients with hemorrhage only into the cerebral substance. Intracerebral hemorrhage is more likely in a patient in whom nausea and vomiting develop with the deficit or in whom there is a rapid lapse into coma. There are no other reliable clinical indicators to distinguish an ischemic infarct from a hemorrhagic infarct. For this reason, further studies need to be done. In intracranial hemorrhage the cerebrospinal fluid will be bloody or show xanthochromia in 75 to 80 percent of patients. Computerized axial tomography will show intracerebral bleeding in most patients. Unfortunately, in at least 10 percent of patients with significant intracerebral hemorrhage, the condition will not be detected by a combination of these clinical and laboratory criteria.

Evidence for the effectiveness of anticoagulant therapy for completed stroke and stroke-in-progress has been contradictory. Howell and coworkers reported that recurrent infarction developed in 7 percent of 103 patients who received anticoagulation therapy, while in a control group of 92 patients recurrent infarction developed in 30 percent. On the other hand, in a cooperative study by Baker and associates the recurrence rate of strokes was 42 percent in patients not treated with anticoagulation and only 27 percent in controls. Recently, in work at the Mayo Clinic, anticoagulants have been used judiciously in the acute phase of ischemic cerebral infarction. Although the results have not yet been reported, there appears to be some indication that the acute use of anticoagulation may be of benefit in preventing the delayed worsening of condition in patients with apparently stable deficits. It is generally accepted that anticoagulation is beneficial in patients with stroke-in-progress. Millikan has reported that progression occurs in 14 to 32 percent of patients receiving anticoagulation and 40 to 64 percent of patients who are not. There are no data available as to the efficacy of aspirin or other agents which decrease platelet adhesiveness in the treatment of acute strokes.

In patients with stroke due to emboli, there is a high incidence of hemorrhagic infarction. Therefore, the best time to begin anticoagulation therapy is approximately seven days after the initial event. Since a profound neurological deficit may develop in patients with repeated embolization, use of acute anticoagulations should be considered. The risk is considerable, but the risk of the devastating deficit is probably higher.

A recent review (Genton and co-workers) of the available literature indicates that anticoagulant drugs have not proved to be useful in completed strokes but are indicated in patients with embolism of cardiac origin.

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Sleep Apnea

THE AMOUNT of hypnotic medication prescribed each year by physicians in this country attests to the prevalence of insomnia and other disorders of sleep. Recently, clinics for diagnosis and treatment of sleep disorders have begun to identify specific causes of insomnia previously unknown or poorly recognized, perhaps the most important being the sleep apnea syndrome, a disorder of both children and adults.

Sleep apnea is a disorder in which episodes of apnea occur as a person is falling asleep. Polygraphic monitoring of patients with this disorder shows that each time electrographically determined sleep occurs there is an apneic episode lasting from a few seconds to about a minute. These periods are terminated by polygraphic indications of arousal, although frequently the patient is not aware of awakening. The spells occur up to several hundred times a night, and result in significant disruptions of sleep and sleep cycles. Insomnia may be the patient's only complaint, but this syndrome is also the cause of significant hypersomnia during the day, often confused with narcolepsy or with psychological disorders.

Most of the apneic episodes are the result of upper airway obstruction caused by hypotonicity of hypopharyngeal muscles, the underlying neuromuscular cause of which is unknown. In a significant percentage of patients with sleep apnea,

systemic hypertension develops as well as pulmonary hypertension, and there are significant cardiac arrhythmias, including ventricular tachycardia, during the apnea. Apnea occurs during inspiration and a salient clinical sign in these patients is the occurrence of loud snoring. A simple screening procedure consists of recording the sound of the patient's respirations during early sleep by means of a cassette tape recorder at the patient's bedside at home or in the hospital. If findings are suspicious, a polygraphic study of nocturnal sleep is indicated. At present no effective drug therapy has been found and treatment consists of tracheostomy, so prompt otolaryngologic consultation is indicated. Symptomatology is totally reversed by this procedure. In the other form of sleep apnea (so-called central apnea), no obstruction is encountered and respiratory effort ceases. In this form of the disorder, tracheostomy is less helpful.

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Lithium Toxicity in the Central Nervous System

LITHIUM CARBONATE is the accepted treatment of acute hypomania and mania. The mild side effects commonly experienced include nausea, vomiting, diarrhea, fatigue and weakness. Polydipsia and polyuria commonly occur and may be due to inhibition of the action of antidiuretic hormone. There may be a fine, mild resting tremor of the hands which is responsive to treatment with propanolol. The serious signs and symptoms of central nervous toxicity of lithium usually appear with serum concentrations greater than 1.5 mEq per liter and include lethargy, lightheadedness and confusion, accompanied by ataxia, drowsiness, slurred speech, tinnitus, blurred vision and profound weakness. The features of severe intoxication are striking and usually appear either over several days of lithium therapy or following an acute overdose. A patient with severe, acute lithium intoxication presents with tremor, increased neuromuscular irritability, increased deep tendon reflexes, nystagmus, confusion and even convulsions. Nonneurologic signs of intoxication include vomiting and acute diarrhea. All of these signs may progress to stupor, coma and eventual death. It is generally thought that life-threatening lithium intoxication does not occur below serum levels of 3.0 mEq per liter. However, the threshold for intoxication may be lowered in elderly patients and in patients taking other medications including the anticholinesterases and haloperidol. There have been some patients with toxic neurologic manifestations in whom serum lithium levels were within the accepted therapeutic range. Alterations in lithium tolerance may be produced by trauma, infection and sodium restricted diets. Severe lithium toxicity has been reported in a woman with a viral infection causing high fever and a serum lithium level of 1.0 mEq per liter.

An electroencephalogram in a patient who is lithium intoxicated may show a variety of changes. Status epilepticus has been reported in previously nonepileptic patients with lithium concentrations in the therapeutic range. The relationship of lithium to seizures was studied in 16 epileptics in whom only one instance of increased clinical seizure activity was reported. In ten of the 16 patients there was a clear reduction in seizure frequency during lithium therapy. The continuous use of lithium for more than eight months has been reported to be associated with increased muscle tone. The development of the altered muscle tone appears to be directly related to the duration of lithium maintenance therapy and is not relieved by benztropine, an antiparkinson drug. Rarely, patients taking lithium can develop choreoathetosis. Patients exposed to elevated lithium levels for prolonged periods have survived with permanent damage to the cerebellum and basal ganglia.

In assessing lithium toxicity, the clinical signs are the most important means of detecting intoxication. Serum levels may be used for confirmation, but it should always be kept in mind that toxicity may occur with serum levels in the therapeutic range. When signs of serious intoxication are noted, lithium administration should be stopped immedately. As a pharmacologically active cation, lithium is not metabolized in the body, but is excreted by the kidneys. The serum half life of lithium is usually about 16 hours. Hemodialysis, or, if hemodialysis is not available, peritoneal dialysis may be used effectively to lower serum lithium levels. Long-duration hemo-

dialysis for 12 to 16 hours will avoid a rebound effect due to the slow movement of lithium between intracellular and extracellular compartments. The usual cause of death in cases of acute overdose is pneumonia or shock. With appropriate attention to cardiac, renal and pulmonary function, and to the maintenance of fluid and electrolyte balance, the recovery of patients with signs and symptoms of acute lithium toxicity will be optimal.

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Syndrome of Infant Botulism

SINCE THE RECOGNITION of infant botulism about a year ago, at least 20 cases have been reported from various parts of the United States. The incidence of the disease process is, therefore, more common than originally anticipated. Both boys and girls who have been previously healthy are affected in early infancy, and over a period of one to two days the ability to suck and swallow is lost, head control is greatly diminished to absent, and the cry is weak. They may be constipated. Cranial nerve abnormalities include ptosis, sluggish pupillary light reflexes, decreased extraocular motility, a paucity of facial mobility and a decreased gag reflex. The muscle tone and stretch reflexes are reduced. Careful electrophysiologic investigation shows small, short motor unit potentials or small compound muscle action potentials (CMAP) amplitude with an increase in CMAP amplitude with repetitive stimulation as has been described earlier in patients with botulism.

The botulinal toxin may not be identified in the serum but the toxin, as well as Clostridium botulism organisms, have been identified in stool specimens. No botulinal toxin has been identified from the stool of clinically normal humans.

The question, of course, is how do infants get botulism? Some of the infant patients were breastfed and others received commercial formula, in addition to a variety of infant foods. The C. botulinum spore is ubiquitous, but after intensive epidemiological investigations, no source of the botulinal toxin has been identified. It has been suggested, therefore, that there may be an *in vivo* production of the botulinal toxin, as shown to occur in other forms of animal life.

Although three known patients have had respiratory arrests, all patients with infant botulism have recovered, receiving general supportive care. None of the patients from California have received antitoxin. There has been no evidence that infant botulism is related to the sudden infant death syndrome.

Botulism should be considered in infant patients in whom there has been rapid onset of weakness, with or without abnormalities of cranial nerve function. Careful electrophysiological investigation should be carried out, and specimens of blood and stool should be sent to laboratories equipped for identification of the botulinal toxin.

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Treatment of Multiple Sclerosis with Adrenal Cortical Steroids

THE CAUSE AND CURE of multiple sclerosis (MS) still elude us and many therapies are used to control the symptoms or slow the recurrent inflammatory-degenerative process. The possible immunological basis of the demyelination has been treated without success by transfer factor, antithymocyte globulin or azathioprine (Imuran®). For several years, adrenal corticosteroids or ACTH have been tried, and it seems appropriate to review the current status of this controversial therapy.

When a patient is in an acute relapse and fails to respond to bed rest and simple supportive

measures, this author uses 40 to 60 mg of oral prednisone or 6 to 9 mg of dexamethasone per day for several days, with eventual tapering of the dose. But what is the evidence that this is helpful when we know that the patient may recover from the attack spontaneously? The long-term use of adrenal corticosteroids has been shown to be ineffective in preventing relapses, but what about short-term use?

In 1970 a cooperative study from ten centers reported that two weeks of therapy with 40 units of ACTH per day led to a slightly greater rate of improvement in MS symptoms and signs than with placebo; but the two groups may eventually have reached a similar late plateau of function. Recent studies of optic neuritis have given similar results. Extensive controlled studies with the orally given preparations have not appeared. The route of administration has been studied. The intrathecal route has been largely abandoned because arachnoiditis with progression of leg weakness has been reported as a possible complication. Furthermore, animal studies show no superiority of that route over oral usage.

Despite the uncertainties regarding the effectiveness of corticosteroids in MS or in related disorders, such as retrobulbar neuritis, the use continues. The final decision on usage in a given case must be a personal one until more rigid guidelines are presented by further studies.

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Progressive Rubella Panencephalitis

RUBELLA, though primarily affecting children, can occur at any age and generally presents as a mild viral exanthem. Greater attention was directed to this viral infection when Gregg intially associated a variety of congenital abnormalities of infants born to mothers who had a history of rubella. These defects included cataracts, microphthalmia, heart defects and failure to thrive. Microcephaly, hydrocephaly, deafness and neonatal thrombopenia were later included as possible congenital defects, and other organ systems have been involved less frequently. Recognition of the influence of the rubella virus on the *in utero* development of the fetus was instrumental in the development of a rubella vaccine, initially licensed in 1969 and now in general usage in the United States.

Our knowledge of the congenital rubella syndrome was expanded when, in 1975, four children were described who had stigmata of the syndrome, but after a period of 11 to 14 years of relative stability, manifested signs of progressive deterioration of neurological function. In three of the four patients there was increase of cerebrospinal fluid IgG with high titers of antibody against the rubella virus. Neuropathological findings in one case were consistent with those seen in patients who had died of active congenital viral infection. Finally, the rubella virus was recovered from the brain biopsy specimen from one of the affected children, suggesting a latent or persistent role for the virus and, indeed, showing similarity to subacute sclerosing panencephalitis — a chronic encephalitis associated with rubeola virus.

In 1974 Lebon reported the case of a 14-year-old boy who had a progressive encephalitis but no known stigmata of congenital rubella; changes in the cerebrospinal fluid in this patient suggested that the progressive encephalopathy was due to rubella or another closely related virus. In another patient, a 19-year-old boy, rubella was acquired when at the age of 7. The patient had good health without known sequelae, until 19 years of age when progressive rubella panencephalitis developed, manifested by dementia, corticospinal and cerebellar dysfunction.

It has become, then, increasingly apparent that infection with rubella virus may produce a wide spectrum of clinical manifestations. Attention is directed to the possibility of progressive panencephalitis being caused by the rubella virus.

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Hydrocephalus in Adults: A Treatable Cause of Dementia

SINCE 1965, when the concept of "normal pressure" hydrocephalus (NPH) was proposed, it has been clear that many adults with a triad of dementia, fluctuating ataxia and incontinence are suffering from this syndrome. Even without a measured increase in cerebrospinal fluid (CSF) pressure, there may be progressive dilatation of the lateral ventricles with associated pressure on the brain tissue of the hemispheres. The block to CSF flow usually is located over the convexities ("communicating" hydrocephalus) and can be caused by scarring from a previous head injury, infection or subarachnoid hemorrhage. In more than half the cases, no obvious cause is apparent.

In separating these cases from cases of dementia due to degenerative processes (for example, Alzheimer disease) or metabolic brain disorders, attention to a history of intermittent impaired alertness, stumbling and lurching ataxia (not clearly a result of some previous central nervous system insult) or indifference to urinary control are suspicious signs. Diffuse "upper motor neuron" signs may be present, such as an exaggerated suck or snout reflex, palmar grasping and Babinski responses. Focal preponderance of weakness can be seen.

Diagnostic tests include computerized tomography (CT scan), which shows the increased ventricles; but this can also be seen in degenerative disease. Therefore the presence of associated sulcus atrophy over the surface seen in degenerations must be carefully assessed. Many CT scan results seem equivocal and consequently tests of CSF flow dynamics also must be done. Cisternography is done by following the movement of isotope injected via a lumbar puncture. The isotope ascends to the head, goes in and out of the ventricles, and over the convexities during 48 to 72 hours. Delayed ventricular clearance and blocked or slowed passage over the convexities suggest NPH. An artificial CSF solution can be safely added at various rates to the lumbar sac to study the compliance and resistance of the CSF space. At a steady pressure plateau the resistance of the space simply is the pressure rise divided by the infusion rate (usually 2.0 ml per minute), and high resistance values correlate well with the other clinical, scan and cisternographic data.

Treatment of NPH by ventriculoatrial or ventriculoperitoneal shunting offers an 80 percent or greater chance of partial to complete reversal of the clinical abnormalities, which means that a vigorous effort should be made to detect this entity in persons who might otherwise be thought to just be becoming senile or have diffuse cerebrovascular disease.

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Carbidopa-Levodopa Combination in Treatment of Parkinson Disease

LEVODOPA HAS OFFERED most patients with Parkinson disease more complete and consistent benefit than any previously used medication. However, for adequate therapeutic effect, large doses are necessary and nearly all patients are disturbed by nausea and vomiting early in the course of treatment, especially as the dose is increased. Between 10 and 15 percent of patients cannot tolerate the gastrointestinal side effects of levodopa and other medications must be used. Other side effects such as orthostatic hypotension, cardiac arrhythmias, dyskinesias and psychotic episodes are seen less commonly.

Recently the combination of carbidopa with levodopa has helped to alleviate some of the problems of treatment encountered when using levodopa alone. Carbidopa is a nonspecific aromatic amino acid decarboxylase inhibitor which prevents the transformation of levodopa to dopamine in extracerebral tissues but, like dopamine, does not cross the blood brain barrier (BBB). Levodopa does cross the BBB and is available to cerebral tissues where it is decarboxylated to dopamine. Without carbidopa approximately 95 percent of the levodopa is transformed outside of the brain and this resulting dopamine may act both peripherally and centrally in areas where the BBB is deficient to produce side effects. The addition of carbidopa permits a reduction of levodopa dosage by 75 to 80 percent and usually decreases

nausea, vomiting, arrhythmia and, in some patients, the "on-off" effect. Unfortunately, the central side effects such as psychosis and dyskinesias are not improved and often appear earlier in the course of the treatment. The tendency for the development of intolerance or refractoriness to the medication also has not been altered.

At present carbidopa is available only as a combination with levodopa in a one to ten ratio. It is marketed as Sinemet® in two tablet sizes, 10/100 and 25/250 (carbidopa/levodopa). Treatment is usually started with the smaller tablet three times a day and the dose is then increased by a half to a whole tablet every one to three days until adequate therapeutic effect is achieved or patient tolerance is reached. Maximum dosage generally should not exceed the equivalent of eight 25/250 tablets per day. If a patient has been receiving levodopa, administration should be stopped for at least eight hours and therapy with the combination may then be started at a level that provides not more than 25 percent of the previous levodopa.

Whether there is an advantage in using the combination in a patient with Parkinson disease as soon as the diagnosis is made or whether it should be kept in reserve until the symptoms become severe has not yet been clarified. The carbidopa-levodopa combination has not eliminated the use of the anticholinergics, antihistamines and amantadine, which may be prescribed initially or concurrently, and may be helpful in patients who cannot take the combination.

Like levodopa alone, combination carbidopa-levodopa treatment does not appear to alter progression of the basic pathologic changes in the basal ganglia. However, with proper dosage adjustments there may be significant improvement in both the quality and duration of life.

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EDITORIALS

Refractory Anemia

THE TERM "refractory anemia," although in usage a long time, must be confusing to those who are not hematologists. It might be well to define it, because it means more than what it says, and to briefly review its history.

Strictly interpreted "refractory anemia" refers to those anemias unresponsive to all known therapy except transfusions. The term "refractory anemia with cellular or hypercellular bone marrow" is used to exclude aplastic anemia. The diagnosis of aplastic anemia now requires a hypocellular or aplastic bone marrow, except in the very early and transient developmental stage.[1] In practice, refractory anemia with cellular or hypercellular bone marrow is used to include those patients with not only anemia but also with pancytopenia and with or without splenomegaly. The term as used excludes those types of anemia with a "known" cause, such as the anemia of chronic disorders, the anemia of liver disease and the anemia of renal failure, even though they are refractory to therapy. It has also been the custom to exclude those anemias that can be sorted out on the basis of morphological criteria—as, for example, dyserythropoietic anemia and sideroblastic anemia, even though they may or may not be refractory to therapy.

It is no wonder then that the "refractory" anemias continue to intrigue and challenge hematologists. They are what is left after all known causes of anemia are subtracted. They represent the frontier in hematologic classification and description. Gradually the frontier is pushed back by the immigration of knowledge—but always a frontier remains.

Refractory types of anemia were defined in 1941 by Bomford and Rhodes,[2] redefined in 1960 by Vilter and co-workers,[3] and now again defined by Geschke and Beutler in this issue.

With the widespread application of bone marrow aspiration and then needle biopsy studies in the first half of this century, the bone marrow infiltrative diseases—leukemia, lymphoma, multiple myeloma, metastatic diseases, myelofibrosis, granulomatous diseases and most recently "hairy-cell leukemia"—were subtracted. The list of subtractants has now become formidable—iron-deficiency anemia, vitamin B_{12} deficiency, folate deficiency, the hemolytic anemias including paroxysmal nocturnal hemoglobinuria. Erythremic myelosis and the De Guglielmo syndrome were defined. Dyserythropoietic anemias were sorted out on the basis of multinuclearity, karyorrhexis, and other bizarre abnormalities of erythroid precursors.[4] Finally, the sideroblastic types of anemia were delineated and subtracted on the presence of "ringed" sideroblasts in the bone marrow.[5] In these anemias about 50 percent of the normoblasts are ringed sideroblasts. The anemia is dimorphic with a small population of hypochromic erythrocytes and a predominant population of macrocytes. Characteristic stippled-hypochromic-macrocytes may be present in the blood smear. The serum iron concentration and transferrin saturation are usually increased.[6]

Geschke and Beutler report on 27 patients with "refractory anemia and hypercellular bone marrow." Thirteen had sideroblastic anemia. Fourteen had no distinguishing characteristics. The two groups could be distinguished only on the basis of the presence or absence of ringed sideroblasts in the bone marrow. Both groups were equally refractory to therapy. The transfusion requirements were similar as were the survival time and propensity to terminate in leukemia. Unfortunately, no mention is made of the red cell morphology on the blood smear in either group.

Geschke and Beutler show that even after all of the above subtractions, "refractory anemia with hypercellular marrow" still exists.

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CME and the Medical Schools

MEDICAL SCHOOLS throughout the nation are beginning to assess, or reassess, their role and responsibility for the education of practitioners—or what is more commonly called continuing medical education (CME). This reevaluation is coming about partly as a result of a growing recognition that practitioner education is indeed part of a continuum of medical education which begins in medical school — or before — and continues through a lifetime of professional practice. But also it is occurring because of increasing professional and public concern with the continuing competence of practicing physicians in these times of rapid progress in medical science and rapid change in medical practice. Both the administration and the faculties of medical schools are becoming increasingly aware of the extent of the contribution of medical schools and their faculties to CME, whether under the auspices of the medical schools or not. And the fact that at least 16 states now require CME for physician relicensure has drawn the attention of the medical school faculties in those states to CME in a very personal way.

In California the Medical Injury Compensation Reform Act of 1975 (AB 1xx) requires that physicians have continuing medical education as a requirement for relicensure. In the wording of this law, continuing medical education is linked to continuing professional competence, to the physician's individual practice profile and to quality review, which in turn is again linked to CME. If one thinks about what these words mean and what these linkages entail, one senses that the enactment of this law may mark the beginning of a new era for CME. It asks CME to do some things it does not yet know how to do, but must learn to do, if it is to fulfill the public expectation of quality assurance in a physician's practice.

There are many actors on the CME stage. In the center as the main focus are the practicing physicians. But also on stage are professional associations, specialty societies, the public in the form of licensing boards, and medical school faculty members. The medical schools themselves may be thought of at present as being somewhere in the wings, perhaps getting ready to come on stage. It is noteworthy that each of the actors plays a lead role during some part of the CME scenario.

It seems likely that medical schools will soon come onto this stage and that they too will have a lead part to play. It seems certain that the role will require greater collaboration with the other actors than has been the case to date. Medical schools seem particularly qualified to help determine what new knowledge should be incorporated into practice, what is obsolete and should be discarded, and what remains current and should be affirmed. Medical schools can contribute a great deal to a better understanding and definition of physician competence, to the development of better educational methods and to research in quality assurance. But each of these will require substantial collaboration and interplay with the other actors on the CME stage.

In a sense, in developing their role in CME the medical schools may become like Janus, looking two ways at once—on the one hand studying and teaching in the world of science, and on the other studying and teaching in the world of practice. A great spin-off would be that practitioner education would affect undergraduate education as well as vice versa, with CME the conduit in both directions.

—MSMW

Management of Diabetic Ketoacidosis in Children

DEATH IN CHILDREN AND ADOLESCENTS with diabetic ketoacidosis is uncommon, provided early and appropriate treatment is given. Mortality in children has been attributed to cerebral edema[1,2] and inadequate replacement of potassium deficits.[3] One approach to reduce mortality is a modification of insulin dosage. Claims have also been made that morbidity of such patients is also lessened.

As reported in this issue by Kaufman and co-workers, the use of small doses of insulin, which are administered by continuous intravenous infusion, has achieved impressive results in the treatment of diabetic ketoacidosis in children[4-7]

Kaufman and co-workers, and other proponents of low-dose insulin, claim that its major benefits

are the minimized risks of hypoglycemia, hypokalemia and cerebral edema. The simplicity and safety of continuous intravenous infusion of small amounts of insulin and, theoretically, the attainment of physiologic blood levels of insulin have also been suggested as additional advantages of this treatment. It has been argued,[8,9] however, that although the serum concentrations of insulin resulting from the administration of "large" doses of insulin may exceed the levels required by peripheral tissues of normal persons for maximal insulin action, the attainment of supranormal blood insulin levels may be necessary to reverse increased hepatic gluconeogenesis and ketone production of diabetic ketoacidosis because the concentration of insulin normally perfusing the liver is substantially greater than that perfusing peripheral tissues.

In more than 1,800 patients with diabetic ketoacidosis admitted to the Childrens Hospital of Los Angeles (CHLA) since 1959, and treated with "large" doses of insulin,[10] the mortality approximated 0.2 percent. Because our results have been extremely satisfactory, we continue to use "large" doses of insulin (0.25 to 2 units per kg of body weight) subcutaneously as the initial dose, based on the degree of ketoacidosis and the blood glucose concentration.[10]

Although only a relatively few cases of children successfully treated with the small-dose continuous insulin infusion method have been described,[4-7] the results suggest that "small" doses of insulin may be equally effective as "large" doses. In comparative studies using different insulin regimens, small intravenous doses of insulin did not appear to be superior to conventional treatment with large doses.[7,11] In addition, the mode of administration of insulin probably does not make a significant difference in the outcome of therapy in most children and adolescents with diabetic ketoacidosis.

Factors other than insulin dose and method of administration that are essential to successful treatment include a physician experienced in the care of seriously ill diabetic children, prompt and appropriate replacement of fluid and electrolyte deficits, and making individual treatment adjustments after careful and close monitoring of the patients' clinical status.

Dehydration is always present in patients with moderate to severe diabetic ketoacidosis. In addition to requirements for maintenance fluid and electrolytes, fluid replacement should be carried out according to the degree of dehydration.[10] Hypokalemia may occur during treatment of diabetic ketoacidosis if potassium is not administered intravenously. In a recent study, potassium requirements were identical whether low-dose or large insulin doses were given.[11] All patients have depleted body stores of potassium and should receive early and continuous potassium replacement at a minimal rate of 3 mEq per kg of body weight per 24 hours, given intravenously. In some patients, particularly in those with a low serum potassium concentration (that is, $K_s < 4.0$ mEq per liter) on admission, the infusion of large amounts of potassium has been lifesaving.[10] In instances when the rate of potassium administration recommended above is exceeded, continuous electrocardiographic (EKG) monitoring should be used to observe for signs of potassium toxicity.

Complications secondary to the administration of sodium bicarbonate cause greater problems in diabetic patients than its omission, particularly when it is infused rapidly or in large quantities.[10] These complications include: (1) life-threatening hypokalemia; (2) tissue hypoxia, due to an increase in the affinity of hemoglobin for oxygen secondary to decreased red cell 2,3-diphosphoglycerate (2,3-DPG) content, which occurs following correction of the protective effect of acidosis; (3) increased plasma osmolality, and (4) central nervous system deterioration associated with elevation of plasma pH accompanied by an exaggerated fall in cerebrospinal fluid pH.

Because severe acidosis may result in diminished functions of the respiratory center and the myocardium, we administer 3.3 ml per kg of body weight of 7.5 percent sodium bicarbonate solution intravenously *over 12 hours* only in patients with severe diabetic ketoacidosis ($pH \leq 7.1$). The blood pH and carbon dioxide content are monitored frequently and administration of sodium bicarbonate is discontinued when the pH exceeds 7.1. We have not observed any harmful effects while following this approach. It is important to note that with the administration of insulin and fluids alone, the serum concentration of bicarbonate is being restored to normal.

Kaufman and his co-workers recommend the use of Ringer's lactate for correction of fluid and electrolyte deficits of their patients despite their strong arguments against the use of sodium bicarbonate. It should be emphasized, however, that approximately 28 mEq of bicarbonate result from each liter of Ringer's lactate.[12] Consequently,

in effect, sodium bicarbonate is being given. The administration of Ringer's lactate may have the same potential for complications as does sodium bicarbonate.

The administration of potassium in the form of potassium phosphate is also advised by Kaufman and his co-workers. This recommendation is logical because phosphate depletion is significant in diabetic ketoacidosis. The consequences of hypophosphatemia are partly reflected by deficiency of 2,3-DPG. However, the need for supplemental phosphate in the treatment of diabetic ketoacidosis has not been thoroughly investigated and phosphate solutions have usually not been administered to such patients at CHLA.

Acute cerebral edema has been an almost uniformly fatal complication of diabetic ketoacidosis in children and adolescents.[1,2,10] Although its pathogenesis is not fully understood, rapid return of the blood glucose concentration and pH to normal, increase in the polyol-pathway activity, insulin-induced alterations in intracellular binding of electrolytes in brain and excessive rates of intravenous fluid administration have been implicated.[1,2,10] It is probable that no single factor is responsible. It is our practice to administer glucose-free solutions if the blood glucose level exceeds 500 mg per 100 ml, to administer 5 percent glucose when the blood glucose concentration is less than 500 mg per 100 ml, and to give 10 percent glucose when the blood glucose level falls to 250 mg per 100 ml or less. No instance of fatal cerebral edema due to diabetic ketoacidosis has occurred at CHLA since 1965 following our treatment regimen.[10] Hypoglycemia resulting in prolongation and exacerbation of the ketoacidotic state has also been avoided by these recommendations. The rate of fall of plasma glucose was the same when the results of smaller doses of insulin were compared with results of larger doses.[7,11]

The goals of treatment of diabetic ketoacidosis are to control the diabetic state promptly with insulin and to restore deficits of water and electrolytes with the administration of intravenous fluids and electrolytes. In the hands of experienced physicians, the use of "small" or "large" doses of insulin appears to be equally effective in achieving a satisfactory outcome. Regardless of the insulin regimen, hypoglycemia and hypokalemia may occur. Blood glucose, potassium and pH must be measured frequently to assess whether the amount and rate of administration of glucose, fluid, electrolytes and insulin require readjustment. The successful management of diabetic ketoacidosis appears to depend more on the quality of care and how well therapy is individually tailored to each patient than on any specific form of treatment currently available.

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Force and Counterforce

THE HARSHNESS of Secretary Califano's recent statement before the AMA House of Delegates in San Francisco sharpens further the adversary relationship which has been developing for some time between medicine and the health care system on the one hand, and our government on the other. The Secretary implied nothing less than that the federal government has determined to use whatever force is necessary to bring the medical profession to the federal heel and health care costs to federal control. His assumptions appeared to be that the federal government has the power to do this, that there will be no opposition to doing it (except from doctors who number only one in a

thousand of the population), and that the federal bureaucracy can in fact control health care costs and still provide the services our citizens expect and to which they have a right (according to the federal edict)—especially when they, the citizens, are sick or believe themselves to be so.

Any threat or use of force gives rise to the possibility and often a pragmatic need for a balancing counterforce. And so it would seem the time has come for medicine and the health care system to develop some counterforce in the public arena. To date the strategy and tactics (such as they have been) have been mostly defensive, responding with defensive measures at various points of attack as these have appeared. The overall result has been a general retreat, with victories infrequent and usually short-lived. Few of the pressing problems have been solved, in fact they have been intensified and a great deal of position and territory has been lost.

The Secretary threw down a gauntlet. He proposes to use whatever force is necessary to achieve the government's purposes. A spokesman for the AMA is quoted as responding by calling on organized medicine to unite in its opposition to governmental bureaucracy as a "cancerous, relentless, mindless blob of a force that oozes through the cracks and seeps under the doors, and as soon as you stop it in one direction it creeps in on you from another." But is this sort of picturesque rhetoric the kind of counterforce that is needed? Organized medicine is already united in opposition to governmental bureaucracy in health care, if in nothing else, and much of the country feels the same way. But to be united is one thing and to do something about it is another. Where is the counterforce, or where are the counterforces that will undermine the strength of the power which is being exercised in so cavalier a fashion? Where are the better solutions, or even better approaches to solutions, for the evident and pressing problems in health care which are at the real root of it all?

An adversary situation between government and the health care system has developed. A callous and impersonal bull, in the form of federal determination and federal regulation, is about to smash its way into a china shop of delicate, often costly, and very personal human needs and human relationships of the citizenry of this nation. Only havoc can ensue. Both in nature and among men, force must give rise to counterforce if there is to be any kind of stability. What might be such a counterforce? The federal bureaucracy has many soft spots, many weaknesses. There are many skeletons in its bureaucratic closets; sluggishness, inflexibility and unresponsiveness are fatal flaws for the regulation of anything so personal and sensitive as health care. Public ridicule is the nemesis of any government bureaucracy. Public exposure to ridicule of some of the skeletons, the weaknesses and the failures might well turn the federal monster in upon itself, consume much of its energy in trying to cover up for its failings, and so greatly weaken its destructiveness in the china shop.

But this alone will not be enough, even if effectively accomplished. A further counterforce will be needed. The health care enterprise will need to develop its own solutions to the evident and pressing problems—solutions that it can live with and make work to solve the problems. And to do this it will need the help rather than the domination of government. The bull must be tamed. The adversary relationship of medicine and the health care system on the one hand and our government on the other must sooner or later be discarded by both parties in the interests of patients who need care and citizens who may become patients. Force and counterforce are not the real answer. Both produce havoc in the china shop—the havoc of expensive and destructive waste. But this is what is happening now and it bodes to continue until emotion subsides and greater reasonableness is restored.

It would appear that the long-range strategy should be to agree that the public and private sectors of society must work together with genuine openness, candor and cooperation. It should be agreed that there are problems, what the problems are and on how best to approach the problems, without destroying in the process too many of the priceless articles in the china shop—delicate and costly human needs and human relationships which we call health care. The sooner this step can be taken the better it will be for the people of this nation. The leadership must come from the private sector and from government. Will it? The situation calls, yes cries out, for a high order of professional and public approval — and thanks — for these statesmen.

—MSMW

CASE REPORTS

Refer to: West SE, Goodkin R, Kaplan AM: Neonatal Salmonella meningitis complicated by cerebral abscesses. West J Med 127:142-145, Aug 1977

Neonatal Salmonella Meningitis Complicated by Cerebral Abscesses

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THE SALMONELLA GROUP of bacteria is an unusual but well documented cause of meningitis in infancy.[1-4] Mortality in the neonatal period is high, and the clinical course is frequently prolonged and characterized by relapses during or following appropriate antibiotic therapy. Acute neurologic complications associated with Salmonella meningitis are not uncommon and include ventriculitis,[5-8] subdural empyema,[9,10] hydrocephalus[6,8,11] and, rarely, cerebral abscesses.[12,13]

This paper reports a case of Salmonella worthington meningitis with multiple cerebral abscesses in a neonate. The infant nine months after completion of treatment is developing normally without apparent neurologic residua. The importance of prolonged antibiotic therapy, awareness of the neurologic complications especially in cases of relapse or failure of conventional therapy, and the need for early and appropriate surgical management of these complications are stressed.

Report of a Case

A 3-week-old infant was transferred to the St. Joseph's Hospital with a diagnosis of neonatal meningitis.

The infant was born at term to a 21-year-old mother. The labor and delivery were normal, and the immediate postnatal course was reported to be uncomplicated. Apgar scoring was 9-9 at one and five minutes respectively, and the birth weight was 3,150 grams.

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ABBREVIATIONS USED IN TEXT

CNS = central nervous system
CSF = cerebrospinal fluid
LP = lumbar puncture
PMN = polymorphonuclear leukocytes

At approximately 3 weeks of age the infant became irritable with fever, vomiting and increasing lethargy. When seen in an outlying hospital emergency room, the infant was described as ashen and extremely lethargic. There was generalized seizure activity. On lumbar puncture (LP), a cerebrospinal fluid (CSF) pleocytosis with evidence of Gram negative rods was noted, and the patient was transferred for further treatment and evaluation.

General physical examination on admission revealed the patient to be obtunded with intermittent focal seizure activity involving the right forearm and hand. The pulse rate was 204 beats per minute; respirations 50 per minute; temperature 38.4°C (101.1°F). Weight was 3,685 grams. The fontanelle was tense, and the head circumference was 38 cm. Tympanic membranes were normal. The neck was stiff, and a positive Kernig's sign was present. The lungs were clear to auscultation, and cardiovascular examination showed a tachycardia without murmurs. Peripheral pulses were diminished. On neurologic examination, generalized increased tone and intermittent extensor posturing were present. The cranial nerves were normal with full ocular movements. Moro, suck and grasp reflexes were sluggish. The deep tendon reflexes were 3+ bilaterally and symmetrical, and Babinski signs were equivocal.

Initial laboratory studies gave the following values: hemoglobin, 13.7 grams per 100 ml; hematocrit, 43 percent; leukocyte count, 2,500 per cu mm with 23 percent polymorphonuclear leukocytes (PMN), 20 percent band forms, 23 percent metamyelocytes and 26 percent lymphocytes. Platelet count was 149,000 per cu mm. The serum sodium level was 128 mEq per liter; potassium, 5.9 mEq per liter, carbon dioxide

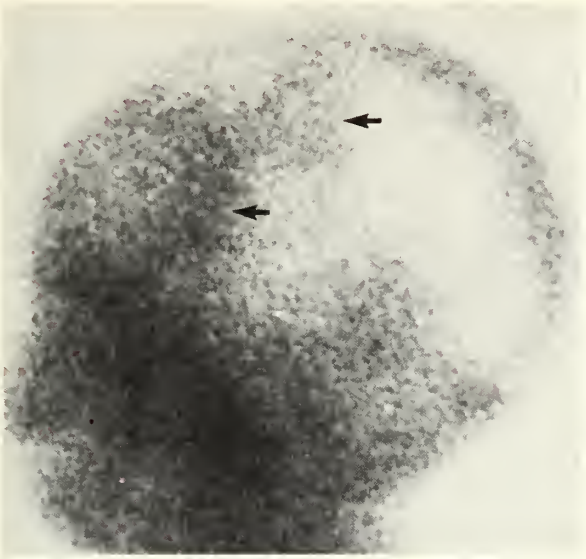

Figure 1.—Isotope brain scan **(left lateral view)** showing multiple abscess cavities **(arrows).**

Figure 2.—Left carotid angiogram **(lateral view)** showing neovascular rim of abscess **(arrows).**

content, 13 mEq per liter; calcium, 9.6 mg per 100 ml; blood urea nitrogen, 11 mg per 100 ml, and glucose, 98 mg per 100 ml. Repeat LP showed 10,000 red blood cells per cu mm and 3,690 leukocytes per cu mm with 85 percent PMN and 15 percent lymphocytes. The CSF protein was 360 mg per 100 ml; CSF glucose, 3 mg per 100 ml, and Gram negative rods were seen on Gram stain. Cultures of blood and CSF grew Salmonella worthington. Initial brain scan with technetium Tc 99m diethylenetriaminepentacetic acid (DPTA) showed an abnormal paramidline accumulation of radionuclide felt to be within the lateral ventricles. There was no evidence of subdural effusion.

Hospital Course

Administration of ampicillin (200 mg per kg of body weight per day) intravenously and gentamicin (7.5 mg per kg of body weight per day) intramuscularly was begun pending culture results. The child also was given decadron (0.5 mg per kg of body weight per day) for three days and phenobarbital (6 mg per kg of body weight per day). When the Salmonella organism was identified, administration of chloramphenicol (50 mg per kg of body weight per day) intravenously was begun, and treatment with gentamicin was discontinued. During the first week of therapy, the infant improved clinically, as did results of CSF studies. Cultures were sterile by the fifth hospital day, and after one week of intravenous antibiotic therapy, oral administration of ampicillin and chloramphenicol was started. Three days later fever and irritability reappeared, and repeat LP showed abnormal CSF chemistries, and S. worthington was again cultured. A serum chloramphenicol level at that time was 3 μgm per ml (normal therapeutic levels—15 to 30 μgm per ml). Therapy with intravenously given antibiotics was reinstituted, but there was little clinical improvement. A repeat brain scan showed increased radionuclide activity bifrontally with a third smaller area of increased uptake more posterior on the left side (Figure 1). Cerebral angiography showed bifrontal avascular masses with a neovascular rim in the left frontal region (Figure 2). Needle aspiration bifrontally through twist drill holes produced purulent fluid, and when air was injected into the abscess cavity there was no evidence of ventricular communication. Continuous catheter drainage of the abscess was started and continued for four days until no further purulent material was noted. Although the chloramphenicol level within the abscess was 18 μgm per ml with a simultaneous serum level of 23 μgm per ml, cultures from the abscess grew S. worthington. Intravenous administration of antibiotics was maintained for five weeks during which time the patient gradually improved.

Serial head measurements showed an abnormally increasing occipital frontal circumference, and signs of increased intracranial pressure were noted during the sixth hospital week. A ventriculogram confirmed the presence of a communicating hydrocephalus and a ventriculoperitoneal shunt was established. The subsequent course

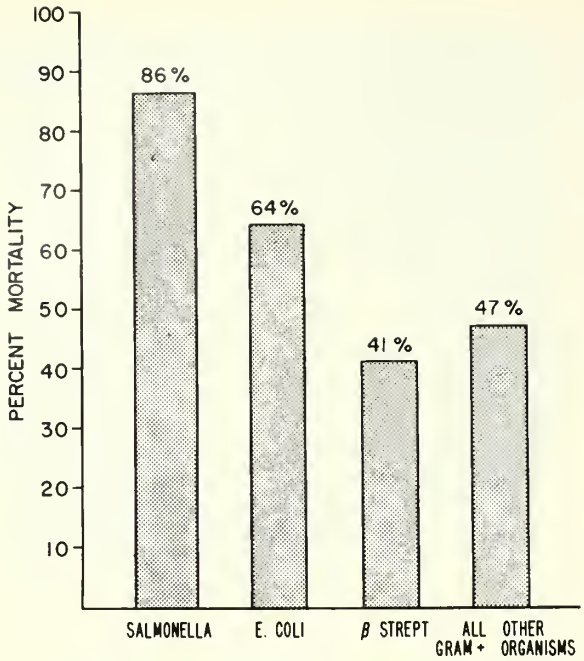

Figure 3.—Mortality ratios of common organisms causing neonatal meningitis.

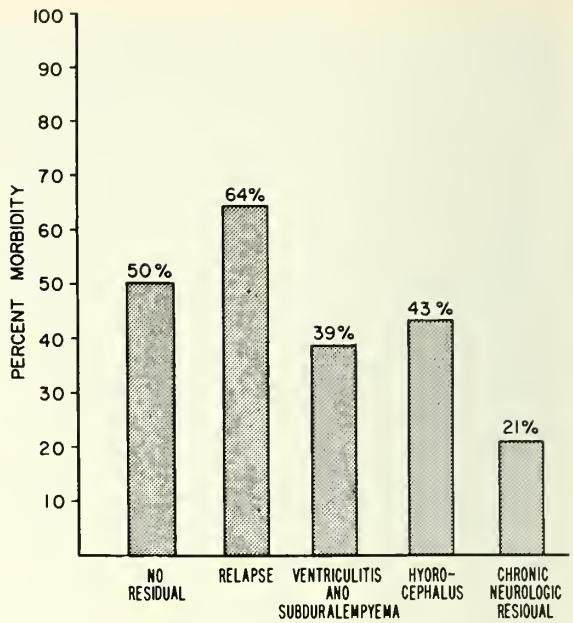

Figure 4.—Morbidity ratios in Salmonella meningitis.

was one of steady improvement, and the infant was discharged on the 71st hospital day.

At 11 months of age the child walks unassisted, has appropriate social behavior and vocabulary, and has no definite localizing neurological residua. Computerized axial tomography showed satisfactory ventricular decompression, and bifrontal low-density lesions were felt to represent residual cavitation from the previous brain abscesses.

Discussion

Central nervous system (CNS) infection is a rare complication of salmonellosis and was first documented by Ghon in 1907.[14] Most patients with involvement of the nervous system are infants, and Henderson's review of the literature[2] on Salmonella meningitis showed that in 83 percent of cases the patients were less than 2 years of age and in 50 percent they were less than 2 months old. Saphra and associates[15] in a review of 7,779 isolates of Salmonella found 77 cases of meningitis, most of which occurred in infants, and Rocha,[3] reporting on 1,727 patients less than 18 months of age, noted 22 with meningitis. These studies approximate a 1 percent incidence of CNS infection.

Although there is no characteristic clinical presentation of Salmonella meningitis in neonates, the prognosis and course differ significantly from other causes of meningitis in this age group. The mortality ratio of 86 percent is higher than that of other common causes of neonatal meningitis[16-21] (Figure 3). In a review of 21 cases from the literature[4-9,22,23] it was found that relapses during or following therapy, ventriculitis, subdural empyema and hydrocephalus were common (Figure 4) and appear to be more frequent than in meningitis due to other organisms. To the authors' knowledge, there have been only two previously reported cases of cerebral abscesses complicating Salmonella meningitis, neither of which occurred in a neonate.[12,13] In the diagnosis of these neurologic complications, brain scan offers a noninvasive means of detecting both subdural effusion and intracerebral abscesses and may even be more sensitive than angiography.[24] In addition, computerized tomography is a useful tool in the diagnosis of hydrocephalus. In view of the high incidence of ventriculitis and the fact that the CSF obtained by lumbar puncture may be sterile in the presence of a ventricular abscess, a ventricular tap should be considered in patients in whom there is poor clinical response to therapy.[25]

Our review of the literature suggests that the medical management of Salmonella meningitis should consist of therapy with appropriate parenterally given antibiotics for at least four weeks. Of patients treated for less than four weeks, relapse occurred in six of seven, while there was recurrence in two of six receiving therapy for more than four weeks. The early surgical manage-

ment of neurologic complications cannot be overemphasized and is felt to have been a contributory factor to our patient's favorable outcome. In regard to the surgical treatment of intracerebral abscesses, various methods have been utilized and include complete extirpation of the abscess,[26,27] repeated aspirations[28] and continuous catheter drainage.[29] The latter was chosen in this case because of the multiple abscesses. Further neurosurgical intervention was not necessary.

Although Salmonella is an unusual cause of meningitis in infants, it should be regarded as an extremely virulent and pathogenic organism with high morbidity and mortality. The patient of this case report is unique because of the occurrence of cerebral abscesses complicating Salmonella meningitis. Despite adequate drug levels within the serum and abscess cavity, the organism continued to grow, reemphasizing the need for prompt surgical drainage. The pathogenesis of the cerebral abscesses is unclear, but may have arisen by (1) hematogenous septic implantation, (2) contiguous spread from the meninges or (3) extension from ventriculitis. In view of the early brain scan abnormality within the ventricular system, the authors would favor the latter alternative as the source of abscess formation.

Summary

A case of Salmonella worthington meningitis in a neonate is reported. Although the disease process was characterized by a relapsing course and complicated by multiple cerebral abscesses, neurologic development nine months after completion of therapy is normal. A review of the literature with emphasis on the neurologic complications, prognosis, and treatment of Salmonella meningitis is presented.

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Dengue Fever in a Western United States City

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DENGUE FEVER is a clinical entity familiar to few United States physicians except those who were in Southeast Asia during the Vietnam war.[1] The endemicity of dengue fever is worldwide, including West Africa, most Caribbean islands, several countries of Central and South America, Polynesia, Micronesia and tropical Asia, as well as Southeast Asia.[2] The last of a series of dengue epidemics in the southern United States occurred in 1941;[2] however, continued infestation of that area with Aedes aegypti mosquitoes, the vector of dengue virus,[3] makes the southern United

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ABBREVIATIONS USED IN TEXT
CDC = Center for Disease Control
CF = complement fixation
CSF = cerebrospinal fluid
DHF = dengue hemorrhagic fever
HI = hemagglutination inhibition
NT = neutralization titer

States a likely locale for recurrence of dengue fever in the future.[2] Because the rapidity of modern travel facilitates the transport of sporadic cases of dengue fever to heretofore nonendemic areas, its diagnosis requires knowledge of the geographical areas of disease endemicity.

In 1963-1964, there were 29 cases of dengue fever imported into this country associated with Caribbean and Venezuelan epidemics.[4-6] Dengue fever has not been reported in the United States since that time, despite a Caribbean pandemic in 1968, and it has never been imported from an area of a Pacific epidemic. This report describes a case in a patient recently seen in Salt Lake City with classical dengue fever after travel to Micronesia.

Report of a Case

On July 11, 1975, a 31-year-old Polynesian man presented to the Salt Lake City Veterans Administration Hospital with complaints of fever and general aches. The patient was a United States citizen who had been in the Tonga Islands since June 3, 1975, and had been well while there. He left Tonga for Salt Lake City on July 5 and stopped in Western Samoa on July 6 and American Samoa on July 7. He recalled a probable mosquito bite on July 6 but remained well until after his arrival in Salt Lake City on July 9. It was noted that there had been an active epidemic of dengue fever (type 2) in Tonga and American Samoa during this period.

The patient became ill at 10 PM on July 10, the day before admission and four days after possible vector exposure. He noted frontal headache with radiation to the occiput, dizziness upon standing and lumbar backache; additional complaints included retrobulbar pain exacerbated by eye motion, a bitter gustatory sensation, photophobia, anorexia and one watery bowel movement. Night sweats without fever occurred on the evening before admission. On the morning of July 11, the patient had generalized weakness and muscle aches accompanied by fever, chills, nausea and a slightly stiff neck. He said that there had been no

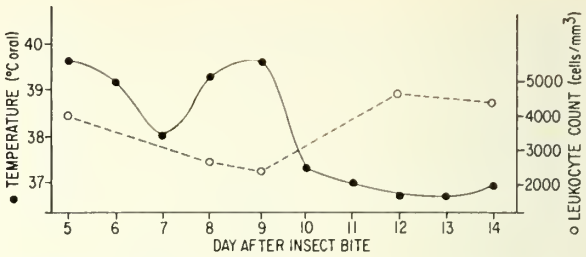

Figure 1.—Temperature and leukocyte count plotted by day after insect bite. Temperature is expressed as the peak on each day of illness.

coryza, pharyngitis, cough, arthralgias, pruritis, rash, dysuria or vomiting. Past history and review of systems were not relevant to the present illness except for a history of yellow fever vaccination in 1966.

On physical examination at admission, the patient was in a toxic condition and febrile. The body temperature taken orally was 38.9°C (102°F) and rose to 39.6°C (102.6°F) within five hours of admission. The patient was normotensive without postural hypotension; a relative bradycardia (pulse 96 beats per minute), scleral injection and shotty cervical adenopathy were noted. Rash, petechiae, arthritis and hepatosplenomegaly were absent. A tourniquet test was negative.

Admission laboratory data included a leukocyte count of 4,000 per cu mm, 87 percent of which were neutrophils, without thrombocytopenia; hemoglobin, 16.1 grams per dl; the admission urinalysis and multichannel chemistry screen gave findings within normal limits; a radiograph of the chest and an electrocardiogram showed no abnormalities. A peripheral smear examination for malarial parasites was negative; a cerebrospinal fluid (CSF) examination gave normal findings. Cultures of blood and CSF for bacteria and fungi were negative. A serum specimen was frozen for serological evaluation and viral isolation.

The patient's febrile course and leukocyte count are depicted in Figure 1. Many of the patient's complaints, as well as fever, partially abated within 48 hours of admission; however, symptoms and fever recurred 48 hours later. Results of repeat CSF examination were again within normal limits; blood and CSF cultures were negative. Additional complaints at that time included pruritis, without rash or petechiae, and diffuse myalgias. A moderate leukopenia (2,400 per cu mm) and mild thrombocytopenia (130,000 per cu mm) were noted, as well as transient elevations of

serum lactic dehydrogenase (370 mU per ml) and glutamic oxalacetic transaminase (152 mU per ml). Another serum specimen was frozen for serological evaluation and viral isolation. While in hospital, the patient's temperature and laboratory abnormalities returned to normal levels. An absolute bradycardia developed, however, and persisted at discharge. Convalescence was marked by arthralgias with ambulation, postural dizziness and weakness for 30 days. No virus was isolated from sera sent to the Utah State Health Department and the Center for Disease Control (CDC). Results of serologic studies carried out by the CDC confirmed the causative agent to be dengue virus (Tables 1 and 2).

TABLE 2.—*Serologic Responses to Other Members of the Togavirus Group**

Serum (date collected)	SEROLOGIC TEST HI YF	HI SLE	HI JEV	CF YF	CF SLE	CF JEV
Acute #1 (7/11/75)	20	10	ND	ND	8	8
Acute #2 (7/16/75)	320	320	ND	ND	128	16
Early Convalescent (8/11/75	320	320	ND	ND	256	16
Late Convalescent (9/19/75)	1,280	160	ND	ND	64	128

*Results are expressed as reciprocal of serum dilution; ND=not done; HI=hemagglutination-inhibition titer; CF=complement fixation titer; YF=yellow fever virus; SLE=St. Louis encephalitis virus; JEV=Japanese encephalitis virus.

Discussion

Dengue fever is caused by a member of the group B togaviruses (formerly the group B arboviruses); four serologic types of dengue virus have been identified.[7] Man is the only known natural host for dengue virus and Aedes species mosquitoes serve as the arthropod vector (A. aegypti in the western hemisphere). After feeding on a viremic human, the female mosquito becomes infectious by bite within eight to 14 days (extrinsic incubation period).[2,7,8] The (intrinsic) incubation period in man averages five to six days (range two to 15 days). The period of communicability from man to mosquito is from one day before to five days after the onset of clinical disease.[8]

This case presents the clinical features of classical dengue fever.[1,2,4,7] A prodrome with conjunctivitis and coryza may precede the typical clinical syndrome by one to two days. Onset is marked by constitutional complaints of malaise, prostration and anorexia associated with headache, retrobulbar pain which increases with ocular motion, lumbar backache ("breakbone fever"), gustatory alterations and myalgias. Physical signs include a sustained or biphasic fever of three to six days duration; general lymphadenopathy; either a diffuse, erythematous mottling rash or a truncal, maculopapular rash; and bradycardia, initially relative, but absolute during convalescence. Less commonly observed signs and symptoms include petechiae with or without a positive tourniquet test, hepatomegaly with or without biochemical evidence of liver dysfunction, arthralgias, gastrointestinal or genitourinary complaints (or both); central nervous system or myocardial involvement rarely occurs.[2,9] Leukopenia (primarily neutropenia) with mild thrombocytopenia is a frequent hematologic abnormality. Classical dengue fever has a low case fatality of 0.1 to 1.0 percent; therapy is generally supportive. Convalescence is marked by prolonged asthenia.

Two other forms of dengue fever are also recognized: "atypical" dengue fever and hemorrhagic fever with or without shock. The "atypical" disease is a mild form of classical dengue fever, resembles an upper respiratory syndrome and may easily be mistaken for influenza or measles.[2,10] In contrast, dengue hemorrhagic fever

TABLE 1.—*Serologic Responses to Dengue Virus, Types 1→4**

Serum (Date collected)	SEROLOGIC TEST HI Den-1	HI Den-2	HI Den-3	HI Den-4	CF Den-1	CF Den-2	CF Den-3	CF Den-4	NT Den-1	NT Den-2	NT Den-3	NT Den-4
Acute #1 (7/11/75)	10	40	20	ND	8	8	8	8	10	10	10	10
Acute #2 (7/16/75)	640	320	640	ND	32	128	64	8	160	1,280	640	80
Early Convalescent (8/11/75)	640	1,280	1,280	ND	32	128	128	8	640	2,560	1,280	160
Late Convalescent (9/19/75)	320	640	ND	ND	64	128	128	128	320	1,280	640	160

*Results are expressed as reciprocal of serum dilution; ND=not done; HI=hemagglutination-inhibition titer; CF=complement fixation titer; NT=neutralization titer by cell culture viral plaque reduction; Den=dengue virus.

(DHF), which is seen most commonly in Oriental children, consists of an early influenza-like syndrome, followed in two to four days by abrupt clinical deterioration accompanied by hemorrhagic phenomena and, occasionally, vascular collapse.[2,7,11-13] Case fatality rates range from 5 to 7.5 percent. Its pathogenesis is not well understood,[11] but DHF resembles a more severe form of classical dengue vasculitis pathologically[7] and may involve complement depletion.[13]

The pathophysiology of classical dengue fever is believed to involve viral uptake and replication in the reticuloendothelial system after mosquito bite.[14] Release of progeny virus and cellular products results in viremia and fever. A secondary viral proliferation in other sites may account for the recrudescence of fever in a "saddleback" fashion. Microscopic evaluation of biopsy specimens of skin lesions shows small blood vessel involvement with perivascular edema, mononuclear cell infiltration and endothelial swelling.[7]

The differential diagnosis of classical dengue fever includes togavirus diseases with similar clinical presentations: chikungunya, O'nyong-nyong and mayaro fevers, sand fly fever, yellow fever and Colorado tick fever. Scrub typhus, malaria, typhoid fever, influenza, measles and, occasionally, viral hepatitis also enter the differential diagnosis.[2,4] Travel history may help to eliminate some of these entities but diagnosis ultimately rests upon results of appropriate laboratory studies.

The laboratory diagnosis of dengue fever involves virus isolation and serologic studies. Virus may be isolated from serum during the initial three to five days of the disease or from mosquitoes captured in the patient's surroundings.[7] Precipitating, hemagglutination inhibition (HI), complement fixation (CF) and neutralization titer (NT) antibody responses to dengue virus infection may be helpful in establishing a diagnosis. Recent attempts have been made at rapid diagnosis employing counter-immunoelectrophoresis for detection of precipitating antibody.[19] HI and, to a lesser extent, CF responses show broad cross-reactivity ("dengue pattern" of response) with other group B togaviruses.[7,15-18] The NT antibody titer is the most specific of these serologic tests and may differentiate the four dengue types. Immunity to dengue fever is type specific and long-lasting; heterotypic protection is short-lived.[2,7,8]

The results of the serologic studies done upon sera from the patient presented in this report (Tables 1 and 2) show definite evidence for a recent dengue virus infection. Although all three serologic tests show responses to at least three dengue virus types, the marginally higher NT antibody response to dengue virus type 2 suggests infection with this virus; the patient's recent travel to Tonga and American Samoa at a time of a dengue virus type 2 epidemic further supports this suggestion. No HI, CF or NT antibodies were induced to three common group A American arboviruses—Eastern, Western or Venezuelan equine encephalitis viruses (results not shown). The broad cross-reactivity of all three serologic tests to all four dengue types, as well as St. Louis and Japanese encephalitis viruses, is typical of the so-called "dengue pattern" of response.[15] Additionally, a broadened serologic response of equivalent titer to numerous group B togaviruses has been associated with yellow fever virus vaccination and dengue virus infection,[20,21] as occurred in this case.

Between 1827 and 1941, there were at least ten documented or suspected dengue epidemics in the southern United States involving Florida, Georgia, South Carolina, Alabama, Louisiana and Texas.[2] Except for cases imported in 1963-1964[4-6] and the one presented in this paper, dengue fever has not been reported in the United States since 1941. Dengue's short incubation period and clinical course has not favored its introduction into the United States and the absence of Aedes mosquitoes in northern latitudes has confined previous epidemics to the southern United States. Rapid world travel, the abundance of Aedes mosquitoes in southern states and the survival of this arthropod during airline flight for three or more days[2,3] make real the possibility of reintroduction of dengue virus into this country, however.

The significance of this case report lies in emphasizing the continued need for physicians to acquaint themselves with infectious diseases endemic to other geographic areas, as well as to acquire a travel history from a patient with a febrile syndrome. Additionally, public health precautions necessitate isolation of a patient with a possible arthropod-borne disease during the period of infectivity for a potential vector.

Summary

A 31-year-old man returning from Micronesia presented in Salt Lake City with signs and symptoms compatible with classical dengue fever. These

included fever, weakness, headache, retrobulbar pain, gustatory alterations, lumbar backache and myalgias. A saddleback fever and leukopenia were documented during the course of the illness, and results of serological evaluation confirmed the causative agent to be a dengue virus. Dengue fever is rarely seen in the United States, despite its worldwide endemicity and the continued infestation of the southern states with its vector, Aedes aegypti mosquitoes. However, the rapidity of modern travel readily allows for the introduction of sporadic cases. This report emphasizes the continued need both for the physician to be familiar with diseases endemic to distant locales and for his acquisition of a travel history from a febrile patient.

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Erysipelothrix Rhusiopathiae Endocarditis

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ERYSIPELOTHRIX RHUSIOPATHIAE has been recorded in both humans and animals, dating to 1882 when Loeffler first identified the infection in pigs, calling it swine erysipelas. In 1884 Rosenbach described the cutaneous disease in humans as erysipeloid of Rosenbach.[1] Erysipelothrix infection is quite common in animals, and man's vulnerability appears to result from occupational contacts. In humans, infection is usually a minor cutaneous one caused by contamination of a small cut; only rarely does it produce the complication of bacterial endocarditis. This paper will discuss a case of E. rhusiopathiae endocarditis. Additional comments will be directed towards the nature of the infection in humans.

Report of a Case

A slightly obese 41-year-old commercial fisherman was referred from his local physician for evaluation of progressive fatigue, fever, malaise, dyspnea with minimal exertion, orthopnea, night sweats, pedal edema and lower extremity rash. The patient said that there was no history of previous murmurs, or known rheumatic or congenital heart disease.

On physical examination the patient was tachypneic, tachycardic at 140, with a temperature of

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100.4°F (38°C) orally, and a blood pressure of 160/50 mm of mercury. A seborrheic rash was present on his chest and petechiae were noted over his extremities. One splinter hemorrhage was present. There were no Roth spots, Janeway lesions, Osler nodes or conjunctival petechiae. There was no lymphadenopathy or hepatosplenomegaly. On cardiovascular examination, a diffuse left ventricular lift displaced several centimeters lateral to the midclavicular line was noted. S-1 was soft and S-2 was single. A loud summation gallop was present. A II/VI systolic ejection murmur was evident at the left sternal border and base; a III/VI decrescendo diastolic murmur was present in the aortic area with a radiation along the left sternal border and to the apex.

Laboratory data included an electrocardiogram showing sinus tachycardia and nonspecific ST-T abnormalities; a hematocrit reading of 31 percent; leukocyte count of 9,700 with 91 percent polymorphs, 3 bands and normal red blood cell indices. Reticulocyte count was 2.6 percent and erythrocyte sedimentation rate 64 mm per hour (Wintrobe method). An x-ray study of the chest showed borderline cardiomegaly with increased pulmonary vascularity. Values for creatine phosphokinase, lactic dehydrogenase, serum glutamic oxaloacetic transaminase and electrolytes all were within normal limits. Analysis of urine showed one to five white cells per high powered field with neither red cells nor casts seen. A rheumatoid factor test was positive with a titer of 1:80. Serum electrophoresis showed an elevated gamma globulin of 1.8 percent and depressed albumin of 2.7 grams per 100 ml.

Seven blood cultures, taken upon admission, were positive with Gram-positive to Gram-variable pleomorphic rods morphologically resembling E. rhusiopathiae, which was subsequently confirmed by biochemical tests. Identification of the organism was substantiated by the Center for Disease Control in Atlanta.

Treatment with 18 million units per day of penicillin, digoxin, and intravenously and orally given furosamide was continued for six weeks. At this time blood cultures were sterile, and right and left heart catheterization and selective coronary arteriography were carried out.

On December 30, 1975, aortic valve replacement was done with a 9A - #2320 composite seat Starr-Edwards prosthetic valve. Surgical findings included normal sized ascending aorta and pronounced left ventricular dilatation. The aortic valve had three leaflets and was not calcified. It appeared anatomically normal except for findings of gelatinous vegetations on the ventricular aspects of all three cusps which grossly distorted the valve causing central aortic regurgitation. The patient's immediate and late postoperative course has been uncomplicated and at six month follow-up (June 30, 1976) he was asymptomatic and had returned to full time work as a commercial fisherman.

Discussion

Economically, swine erysipelas is a serious problem in Europe, Asia and North America, costing American farmers approximately twenty-five million dollars annually.[2] One of the major reasons for this economic impact is the ubiquitous nature of E. rhusiopathiae. The disease has been reported in an assortment of wild mammals, various fowl, and many domestic animals including pigs, sheep, cattle and horses. Shellfish, fish and some insects are capable of harboring Erysipelothrix as a commensal, and swine can have a carrier state contaminating barnyards, water supplies and food through fecal spread.[2] The organism is extremely hardy being resistant to pickling, salting and smoking. In nature it has remained viable in a buried carcass for nine months.[2] Schiffman and Black reported the case of a construction engineer infected at the site of a barnyard that had been vacant for a year.[3]

Considering its prevalence in nature and the opportunity for occupational contact, man is fortunately relatively immune to Erysipelothrix. As in swine erysipelas, human infection occurs with greater frequency during the summer months.[9,10] Erysipelothrix infection in man manifests itself in three forms. The first, erysipeloid, sometimes called fish-handler's disease, is a cutaneous infection which occurs at the site of a scratch, injury, or puncture wound usually on the hand or arm.[4-5] Infection from an insect bite has been reported.[6] Symptoms appear in one to five days with intense pain, swelling, itching, and purple-red erythema which extends peripherally as the central area fades. Erysipeloid is characterized by remissions and relapses[4,5] and an absence of suppuration.[7-9] The disease is usually self-limiting with spontaneous recovery common in one to four weeks.

The infection may progress to a more generalized constitutional form characterized by polyarthritis, extensive erythema, swelling and intense

itching, even though the initial cutaneous lesion appears to have healed.[9] With these symptoms, misidentification as rhus contact dermatitis can occur.[10]

The last and most serious form of the disease is endocarditis. The symptoms are those usually seen with subacute bacterial endocarditis including dyspnea, arthralgia, weight loss, fatigue and fever.[9] Murmurs, splenomegaly and petechiae covering the trunk are sometimes noted. Since 1912 a total of 30 cases of human endocarditis or septicemia have been reported.[1-3,7,11-20] In reviewing these cases, several clinical characteristics are significant. The age of the patients ranged from 10 to 69 years, although most were middle aged. A predominance of males is indicative of the occupational hazard presented by this organism. All patients had opportunity for contact with E. rhusiopathiae through their occupations, although in many cases a primary erysipeloid lesion was not observed. Overall, 15 of the 30 died. Seven of these deaths occurred before the advent of penicillin therapy in 1944. The remaining eight deaths are attributed to various physical conditions of the patients. In one woman there were symptoms of subacute bacterial endocarditis for one year before diagnosis, with death being attributed to aortic insufficiency.[2] Presumably normal heart valves, as was the case with our patient, as well as those involved with congenital and rheumatic heart disease seemed vulnerable to endocarditis. Nine of the patients did have an antecedent history of rheumatic heart disease. Frequently underlying these deaths were physical disabilities, as well as alcoholism and poor nutrition, which may have affected the patient's immune response.

In conclusion, E. rhusiopathiae, while a common organism, is not a frequent pathogen. Occasionally a severe form of infection in the form of endocarditis occurs, but this event is rare as shown by the infrequent accounts in the literature.

Summary

A slightly obese forty-one-year old commercial fisherman was referred for evaluation of progressive fatigue, fever, malaise, dyspnea with minimal exertion, orthopnea, night sweats, and pedal edema. Purpuric spots were present on the ankles and hips. Subsequently, seven blood cultures were positive for Erysipelothrix rhusiopathiae. Treatment was carried out for seven weeks with intravenously given penicillin G, 18 million units per day. At this time blood cultures were sterile, and cardiac catheterization was done because of evidence of pronounced aortic insufficiency and left ventricular failure. Aortic valve replacement was recommended based on the catheterization findings. An aortic valve replacement was done and the immediate and late postoperative course was unremarkable.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

FTC and the Professions

To the Editor: The editorial dealing with the Federal Trade Commission and Health in the June issue is a most important warning to the medical profession. There is a danger to the public and the profession of viewing health care as a "business," "industry" or "trade." Too much emphasis on economics in health care places its providers and the public in ever greater political jeopardy.

I am hoping the AMA heeds your warning. From the frequent allusions to health care as an "industry" in the *American Medical News,* I am afraid they themselves contribute to the atmosphere of misunderstanding. I commend you for your thoughtfulness.

EDWARD PALMER, MD
Lake Oswego, Oregon

More on Saccharin

To the editor: I wish to add my views to the discussion about saccharin.

I am dismayed by the stand most physicians and editorials (The Saccharin Affair, West J Med, April) are taking on saccharin and related carcinogens. The FDA has no "ax to grind" other than to make a weak attempt to guard the public's health. Its position is being threatened by industry's onslaught—which is understandable—if not commendable. But why our vehemence?

We as physicians, along with others in the scientific community, know that cancer is becoming an increasingly environmentally produced disease. Currently we are exposed to some 25,000 synthetic chemicals, and approximately 700 new compounds a year are being introduced without prescreening for carcinogenicity (example, Tris in our children's nightwear).

Certain types of chemicals have been repeatedly shown to be carcinogenic: aromatic amines, alklyating agents, nitrosamines, polycylic hydrocarbons—of which coal tars head the list. And saccharin is a coal tar derivative.

It seems simplistic to repeat that rats and humans have the same chemical metabolites, the same covalent bonding which is the necessary precursor to the malignant process, the same target organs. Vinyl chloride carcinogenicity was proven in rats long before it surfaced as angiosarcoma in the human liver. What happens to rats, happens to us.

As to the question of the quantity necessary to produce malignancy in susceptible subjects, there is no test to define the threshold of harmlessness. Oncologists tell us even one cell may generate the fatal process. Effects of carcinogens are dose-dependent, additive and probably irreversible. Although the total daily exposure may be small, it is the total cumulative effect that gives cause for alarm.

Upon whom can we place our reliance for safety and malignancy testing? It would be naive to depend on self-serving industry, which in recent record has deliberately doctored and falsified data regarding toxicity and carcinogenicity of its products—upon whose continued existence its industrial life and stock averages depend. We doctors do not have any national agency for testing products or even drugs—and without FDA warnings we would still be prescribing harmful drugs to our patients daily. Without the FDA we would be returning to days of complete reliance on the PDR and pharmaceutical salesmen as to the safety of products.

Public confidence in the medical profession is at a low ebb. In view of more recent disclosures (bladder cancer via saccharin in men), how can the American people look to us for medical guidance if we continue our present stance?

PAULINE FURTH, MD
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Informed Consent

To the editor: The Special Communication "Informed consent, Is it bad medicine?" by Ronald L. Katz, MD (West J Med 126:426-428, May 1977) and the accompanying editorial "Informed Consent—An Unreality?" (West J Med 126:391, May 1977) should not be allowed to pass without some comment since it may, unintentionally, lead some physicians into serious trouble.

Dr. Katz appears to confuse the obtaining of an informed consent from a patient with the memorializing of that fact by means of a signed special form. The first is a requirement of the law while the second is not. Further, the law insists that a patient be informed at the time he gives his consent and is not concerned with whether or not he remembers at any future time. That question only arises in the event of a law suit and a properly dated and signed progress note by the physician, attesting to the fact that the patient was given adequate information, is felt by most defense attorneys of my acquaintance to be better in convincing a jury than any printed form.

The anecdotal cases cited by Dr. Katz cannot be relied upon for any type of scientific conclusion. It is clear that the reaction of a patient to what is said is dependent to a great degree upon how it is said. The use of terms such as "vivid bad dreams" and "vivid discussion of spinal headache" in "100 percent of his patients" brings into question the "bedside manner" of the physicians involved. The law[1] neither requires a discussion of possible complications which are common knowledge (such as nausea and vomiting following anesthesia), nor any discussion with a patient who clearly states he doesn't want to hear one. My impression is that the physicians involved in these situations were trying, consciously or subconsciously, to evoke as many harmful effects as possible in order to prove to themselves that "the law is an ass."

But however the law of informed consent may be categorized, it remains the law in California, as expounded in *Cobbs vs Grant*.[1] It is not the prerogative of physicians to ignore or avoid this law, or any other law. One may believe that the requirement of a license to practice medicine and continuing medical education to maintain that license is unnecessary or even harmful. Those laws are evaded at the peril of the physician. The law of informed consent is as binding.

As a physician who has practiced anesthesiology for some 20 years I can understand Dr. Katz's reaction and agree that the present law of informed consent needs drastic reinterpretation and liberalization so as to permit physicians more discretion. As a defense malpractice trial attorney I must advise physicians to conform to the present law,[2] or to be prepared to pay the penality for breaking it.

The law is what the Legislature and the Supreme Court say it is, and not what I, Dr. Katz or any other physician would like it to be. To follow Dr. Katz's advice "that we provide patients with reasonable explanations of what *we* feel is appropriate" (emphasis added) is probably asking for trouble under the present status of the law. An idea of what is required may be obtained by reference to *BAJI* 6.11[3] which is the instruction given by the judge to the jury just before it begins its deliberation. It may be found in any law library.

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* * *

Dr. Katz Replies

To the Editor: Dr. Engel and I have disagreed on the issue of informed consent in the past and still do. Each physician must decide for himself or herself how to best respond to the needs of the patient and the confines of the laws.

While I do not remember the physician involved in the "vivid bad dreams" case, I do clearly remember the physician involved in the ""spinal headache" cases. He was a kindly old surgeon whose bedside manner was held up to the medical students and residents as an ideal example. He was literally loved by his patients and was frequently called upon to operate on his colleagues. Thus, Dr. Engel's impression is wrong. The physician described above did not have to prove that "the law is an ass" since in the situation we are discussing that is abundantly clear.

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Trauma Rounds

Chief Discussant
GEORGE H. A. CLOWES, JR., MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Clowes GHA Jr: The role of the liver in recovery from critical injury (Trauma Rounds). West J Med 127:154-157, Aug 1977

The Role of the Liver in Recovery From Critical Injury

ROBERT BURK, MD:* The patient is a 43-year-old man who was a passenger in a motor vehicle that was struck broadside by a fire engine. At the time of admission to the hospital he had stable vital signs but was complaining of chest and abdominal pain. Blood pressure was 170/80 mm of mercury and pulse was 100 beats per minute. He was alert and cooperative. There was tenderness to palpation over the entire right lateral hemithorax with decreased breath sounds in the right lung. The abdomen was slightly distended with tenderness to deep palpation in the right upper quadrant.

Arterial blood gas studies showed a Po_2 of 159 on 40 percent oxygen, a Pco_2 of 38 and a pH of 7.37. On an x-ray film of the chest, fractures of ribs 3 through through 11 posteriorly on the right were seen. There was diffuse haziness of the right lung field. No abnormalities were seen on a plain film of the abdomen and findings on an intravenous pyelogram were within normal limits. The urine was clear.

A tube thoracostomy was done on the right and a small amount of bloody fluid drained. The patient's condition was relatively stable for the first 48 hours after admission, but on the third day a diffuse reticular infiltrate developed in the left lung. An endotracheal tube was inserted and positive pressure ventilation was begun.

Liver function studies at this time showed the following values: total bilirubin, 2.0; serum glutamic oxaloacetic transaminase, 380; lactic dehydrogenase, 130, and total protein, 5.6. Because of the possibility of liver injury, an abdominal aortogram and a liver scan were done; no abnormalities were shown.

The patient remained febrile with temperatures reaching 39.4°C (103°F) daily. Blood urea nitrogen rose to 30 mg per 100 ml and creatinine to 3.5 mg per 100 ml. The patient did not appear to be in a toxic condition. Results of tests of sputum were unremarkable. Blood cultures were repeatedly negative. The patient's hepatic and renal functions remained stable, but pulmonary function deteriorated progressively despite positive pressure ventilation and positive end expiratory pressure (PEEP) therapy.

Because of the absence of specific findings sufficient to account for the patient's clinical course, exploratory laparotomy was carried out on the fifth day after injury. Findings on examination of the liver, pancreas, duodenum and both kidneys were not remarkable. No evidence of intraperi-

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toneal injury was present, but there was a small residual hematoma in the right retroperitoneum. The patient's course continued to deteriorate progressively with the arterial Po_2 dropping to 29. Cardiac arrest occurred 48 hours after laparotomy. Resuscitation attempts were unsuccessful.

On autopsy the lungs were found to be diffusely hemorrhagic; hyaline membranes and acute inflammatory changes consistent with diffuse pulmonary infection were noted. There was no evidence of abdominal sepsis.

F. WILLIAM BLAISDELL, MD:* I would like to introduce Dr. George Clowes, Clinical Professor of Surgery at Harvard Medical School, who has been our Visiting Professor this past week. Dr. Clowes is an established authority on sepsis and septic shock and has been particularly interested recently in the role of the liver in critical surgical illness.

Dr. Clowes, I hope that you will use this case as the basis for discussing the causes of the multiple organ failure syndrome.

GEORGE H. A. CLOWES, JR, MD:† Let's start by reviewing this patient's problems. There was something occurring in the abdomen that suggested a paralytic ileus; there were chemical abnormalities consistent with modest insufficiency of liver function; there was a fever consistent with sepsis. The initial problem was contusion of the right lung, but secondary respiratory distress syndrome symptoms also developed—at first involving only the left side. This pulmonary failure was ultimately responsible for the patient's death.

When on the second or third day after injury, one sees a fever develop that is not accounted for by pulmonary abnormalities, one should immediately suspect some problem in the patient's abdomen—possibly an injury to the intestinal tract or other site of infection such as the retroperitoneal space. This concept is supported by the progress of the lung lesions in this patient. Typically, the secondary lung lesion is initiated by nonthoracic sepsis and I concur with the decision to carry out exploratory laparotomy during the latter phase of the illness.

FRANK R. LEWIS, MD:‡ I was the attending physician on this case. This patient presented an extremely perplexing problem. We felt that there probably was some type of retroperitoneal process occurring, but an intravenous pyelogram showed a normal appearing kidney with no displacement of it or of the ureter. There was possibility of liver injury, but there was only mild elevation of enzymes with maximum bilirubin of 2 mg per 100 ml and negative findings on liver scan and angiogram. A gastrointestinal series also was done to check the condition of the duodenum, but results of this also showed no abnormalities.

His course was not that of a patient with an intraperitoneal hollow viscus injury, for the problem seemed more or less restricted to the retroperitoneum. Ultimately, however, because of the clinical course we felt compelled to carry out exploratory laparotomy. No significant pathology was found nor was there any shown on subsequent autopsy.

I believe that the problem in the case was purely a respiratory one and that the respiratory failure and subsequent demise were secondary to profound respiratory sepsis.

DR. CLOWES: I agree that this patient's death was due to respiratory failure; there was a massive arteriovenous shunt before death and a Po_2 of 29 at the time of cardiac arrest. This shunt approached 50 percent, and shunts of this magnitude are simply not compatible with life. This is, therefore, not the typical case of a patient who dies of multiple organ failure in which every organ system shares in the deterioration of the clinical course. But I shall use this case as a basis for discussion, as Dr. Blaisdell suggested.

In a typical case of multiple organ failure, severe infection has been present for two to three weeks and the patient is in a semistarved state wtih high output circulation but gradually decreasing cardiac output. Renal failure develops and, finally, hepatic failure. This combination of renal and hepatic failures is associated with a mortality rate of nearly 100 percent. Furthermore, the most common predisposing factor in multiple organ failure is overwhelming sepsis; this appeared to be associated with 75 percent of such cases on our service.

I believe that liver failure is the most important aspect of progressive multisystem organ failure and that injury to the liver sets the stage for septic demise. In 286 cases of injured and septic patients carefully studied by myself and my associates during the past 15 years, the overall mortality was 37 percent. However, the mortality rate was 53 per-

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cent in the 98 patients of this group in whom there was evidence of hepatic insufficiency, as indicated by bilirubinemia or elevated enzymes. Furthermore, among the 42 who died with progressive multisystem failure, liver failure was present in 86 percent.

In a smaller group of 41 patients who had suffered trauma and who were in a septic condition, the metabolism of those with normal liver function was compared with that in those whose liver function failed, in order to ascertain what the determinants of death might be. They were divided into four groups: those with no liver impairment who survived (group 1) and those who died (group 2); those with liver failure who survived (group 3) and those who died (group 4). In the preterminal period, no significant differences among the four groups were found in metabolic rate ($+32 \pm 12$ percent), nitrogen excretion (-18 ± 6 grams per day), blood glucose (165 ± 30 mg per 100 ml) or blood insulin values (35 ± 10 μU per ml). On the other hand, the sum of the blood concentrations of branch chain amino acids were below normal (510 ± 168 μM per ml) in all groups, but significantly lower in group 4 (310 ± 95). This finding indicates that the consumption of branch chain amino acids in the skeletal muscles produces a deficit of these amino acids. At the same time, the average albumin level of the blood of 2.4 ± 0.4 in group 4 (lower than in the others) suggests that secretory protein synthesis was seriously impaired.

Just as sepsis is almost always present, malnutrition due to gastrointestinal dysfunction also is inevitably a part of the picture. The result is an energy fuel deficit which in sepsis is usually manifested by a breakdown of peripheral protein structure, particularly in skeletal muscle. Because muscle can only oxidize the branch chain amino acids, muscle protein cannot be resynthesized and all the residual amino acids must be released into the circulation for clearance by the liver. It is in the liver that the amino acid alanine and certain other glycogenic precursors are converted to glucose. This aspect of liver function is preserved in the failing liver almost until death; that is, unless endotoxemia is present to an extent sufficient to inhibit hepatic gluconeogenesis. Continued function of the liver, therefore, is of vital importance.

In addition to the direct effects of trauma, the liver itself may be seriously injured by hypoxia due to reduced circulation or from endotoxin and other toxic agents. Studies carried out in pigs by my former colleague Dr. Immamura showed that in the low cardiac output state, whether caused by hypovolemia or by septic shock, the delivery of oxygen via the hepatic artery is proportionally reduced as cardiac output is decreased.

Work by Dr. Leena Mela at the University of Pennsylvania showed that endotoxin impairs the function of hepatic cell mitochondria, while certain of the peptides we have found block oxidative phosphorylation. Another very important aspect of hepatic injury lies in the effects upon the liver itself caused by failure of protein synthesis due to lack of certain essential amino acids.

DR. BLAISDELL: *Can you prevent this by the exogenous administration of amino acids?*

DR. CLOWES: Unfortunately not always at this stage, because histidine, methionine and the aromatic amino acids are significantly elevated in these patients with evidence of impaired liver function. As you will remember, the aromatic amino acids are precursors of certain neurotransmitter substances and in this state may compete producing neural disorders such as encephalopathy. It is possible, as suggested by Dr. Joseph Fischer of Massachusetts General Hospital, that the administration of branch chain amino acids alone might rectify the situation. Yet, this remains doubtful, since at this point the hepatic cells have degenerated too much for quick recovery to be possible. Studies of the liver in patients after severe prolonged shock by Dr. Trump at the University of Maryland and after severe sepsis by my colleague Dr. Carl Teplitz show the endoplasmic reticulum and the Golgi apparatus to be swollen and disintegrating. Therefore, it appears unlikely that the hepatic cells can synthesize protein in the normal way.

If albumin is administered to a patient in whom there has been a protein deficiency, it rapidly disappears. Albumin serves as a source of amino acid building blocks. However, albumin is an incomplete source since it has no isoleucine. Administering albumin, then, still leaves a deficit of this essential amino acid. But I believe nonetheless that increasing albumin levels is a form of nutritional therapy that may be of value in the short run. You can put albumin into a patient who is hypoalbuminic (for example, one in whom the blood level is 2.0 and, by so doing, bring the blood level up to 3.0), although this does require that you infuse a couple hundred grams of albumin. Despite

the fact that hypoalbuminemia is transiently corrected, the fundamental defect in protein synthesis is not.

DR. LEWIS: I find it very difficult to raise the serum albumin level by administering exogenous albumin since it takes such large quantities before any effect is seen.

DR. CLOWES: That is what I meant when I made the observation that albumin is used as a fuel or for building blocks.

Failure of protein synthesis may be easily recognized by a decline in serum albumin. When a critical level of 2.5 grams per 100 ml in the plasma is reached, the stage is set for catastrophe. Impaired protein synthesis results in loss of immunocompetence and in progressive septic invasion. Wound healing ceases. The induction of enzymes fails and the many other functions of the various organs that are dependent on protein synthesis gradually cease, also. Unless prevented or arrested, this process results in death—usually with overwhelming sepsis, respiratory insufficiency and circulatory failure.

DR. BLAISDELL: *What can we do to prevent liver failure from developing in a patient such as the one presented today, Dr. Clowes?*

DR. CLOWES: The object is to avoid or minimize the injuries which lead to progressive multisystem failure. Of primary importance is the elimination of stimulus. Pus must be drained and devitalized or gangrenous tissue must be resected. From these sites emanates a variety of peptides and other toxic agents which injure the lung, cause myocardial depression and even seriously alter the pattern of energy metabolism.

Injury from inadequate circulatory perfusion due to hypovolemia or sepsis must be adequately treated, too. In complicated injury cases of the type seen today, this usually requires the aid of a Swan-Ganz catheter. The correct fluid volume and atrial filling pressures must be maintained so as to ensure adequate vital organ perfusion (a previous Trauma Rounds dealt with this subject[1]). The key organ in this regard is the kidney, and good renal output means that adequate circulatory resuscitation has been obtained. If myocardial depression is present as manifested by pulmonary wedge pressures above 12 to 15 mm of mercury, with poor peripheral perfusion and low urine output, then administration of ionotropic drugs such as digitalis, isoproterenol or dopamine may be required. It must be remembered that injured patients in a septic condition have a lower-than-normal peripheral vascular resistance. To satisfy the abnormally high circulatory demand, a cardiac output 50 percent or more above the normal resting value must be maintained. This is the pattern of recovery. If other measures fail, we have had surprising success in restoring the high cardiac output with the administration of glucose, potassium and insulin. This in part compensates for a metabolic abnormality of shock—low insulin secretion.

Hypoxemia, with its deleterious effects on tissues, must be averted with the use of respirator and PEEP, if required. Despite the best efforts this treatment may fail as, unfortunately, it did in this case. But without its use the incidence of respiratory failure is much higher.

Of major importance is the maintenance of adequate nutrition and energy production. The objective is to preserve protein structure and protein synthesis. In patients who are seriously injured and in a septic condition, the average excretion of nitrogen is 18 grams per day. This is the equivalent of nearly 120 grams of protein broken down for glucogenesis and ureagenesis. To reverse this process we have found that approximately 20 to 22 grams of aminonitrogen must be supplied. At the same time, the patient's full caloric requirement must be satisfied. This means that between 40 and 50 kilocalories per kilogram of body weight must be supplied, either as glucose alone or as a combination of glucose and lipid suspension. Recently we have had excellent results employing Intralipid®—up to 1,500 ml per day.

In summary, progressive multisystem failure is usually the result of failure of energy metabolism and protein synthesis due to prolonged starvation and sepsis. Hepatic insufficiency for a variety of causes is almost always present. The best treatment is prevention by limiting secondary tissue injury and malnutrition. At times the progress of the illness can be reversed by appropriate supportive measures for all affected organs. But more often than not, the outcome is death, which simply reflects the present "state of the art."

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Refer to: Fine A: Informed consent in California—Latent liability without 'negligence' (Medical Jurisprudence). West J Med 127:158-163, Aug 1977

Informed Consent in California

Latent Liability Without 'Negligence'

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Informed consent is a legal obligation due from a physician to his patient, an obligation which may not be met by the physician's skillful treatment of his patient. It may only be met by the treating physician obtaining from his patient knowing authorization for carrying out the intended medical procedure. The physician is required to disclose whatever would be material to his patient's decision, including the nature and purpose of the procedure, and the risks and alternatives. The disclosures should be made by the physician to his patient, and not through use of consent forms which are not particular to individual patients. To minimize any subsequent claim by the patient that there was a lack of adequate disclosures, the physician should record in the patient's chart the circumstances of the patient's consent, and should not rely on the patient's unreliable ability to recall those circumstances.

THE CONCEPT of informed consent emerged in the early 1900's from legal cases involving circumstances where no consent had been given for the medical procedure done. The most extreme example was a situation in which a patient consented to a medical procedure which was erroneously carried out on another patient, who had never given his consent to any procedure. A more common example was where a patient consented to a particular medical procedure and some other procedure was done. Liability was founded in these cases not on negligent treatment, but on the unconsented-to touching of the patient. The patient never consented to any medical procedure, and yet carrying out any medical procedure necessarily involves touching the patient. The touching, being unconsented-to, was in civil law technically a "battery." No matter how skillfully the unconsented-to medical procedure was done, there was still liability for the unconsented-to and, therefore, wrongful touching or battery. The concept of informed consent was premised on the basic principle that every competent adult has the right to determine what shall be done with his own body. (This principle was first enunciated in 1914

Adapted from a talk given at Surgical Grand Rounds at University of California, Los Angeles, Center for the Health Sciences, on November 17, 1976. The author is Chairman of the Subcommittee on Informed Consent of the Los Angeles County Bar.

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by Justice Benjamin Cardozo, in *Schloendorff v. Society of New York Hospital,* 211 N.Y. 125, 105 N.E. 92 [1914]). Accordingly, no medical procedure may be done on a competent adult without his consent. The concept has two basic elements: first, that the patient is entitled to information on the proposed treatment and, second, that based on that information the patient must consent to the treatment before it may properly be carried out.*

The significance of the lack of informed consent, as measured by the frequency with which it gives rise to malpractice actions, is not clear. There is some feeling that the lack of consent is asserted in a large number of medical malpractice actions because it potentially offers a patient recovery even where there has been no negligence in treatment. In 1973 the Department of Health, Education, and Welfare (DHEW) published an extensive report on medical malpractice, including statistics concerning informed consent.[1] As set forth in that report, since 1961 the concept has become more significant as an issue in malpractice cases. DHEW found that informed consent was an issue in 6.6 percent of all medical malpractice appellate court decisions in the United States during the period 1961 through 1971 and was the most significant issue in 4.7 percent of those same appellate court decisions.

Whatever the significance of the concept may have been nationwide, it received dramatic new impetus in California in 1972 in a landmark decision by the California Supreme Court in *Cobbs vs Grant* (8 Cal. 3d 229; 104 Cal. Rptr. 505, 502 P. 2d 1 [1972]). The patient in that case, Cobbs, had a duodenal ulcer and consent was obtained from him for a vagotomy. When his consent was obtained, he was not informed of the risks of a vagotomy, including the risk of a possible injury to his spleen and possible subsequent development of a gastric ulcer. Both of these things occurred, resulting in a subsequent splenectomy and then a gastrectomy. Cobbs sued his surgeon, Grant. He claimed that Grant had carried out the vagotomy negligently and, alternatively, even if he had not negligently done the vagotomy, he was otherwise liable because no valid consent had been obtained, the consent having been given without disclosure of the risks of a vagotomy. The jury returned a verdict for Cobbs without specifying whether it was based on negligence in doing the vagotomy or on the lack of informed consent. Grant appealed the decision and the Supreme Court reversed it, finding no substantial evidence of negligence and sending the case back to the trial court to determine whether there was informed consent. The Court in remanding the case reviewed the standards applicable to an informed consent and in so doing made significant new law.

The Court first clarified that while carrying out a medical procedure without any consent constitutes a battery, doing it without informed consent constitutes negligence.

The Court then determined that in obtaining an informed consent the adequacy of a doctor's disclosure to his patient is subject to a legal standard and not a medical standard. (Before *Cobbs,* there was a split of authority in California on the applicable standard, most courts holding that a medical standard applied requiring a doctor to disclose only such information as would be disclosed by a doctor in good standing within the medical community [*Cobbs, supra,* 8 Cal. 3d at 241]). According to the Court, a doctor is required to disclose all information relevant to a meaningful decision by the patient, generally including the nature of the proposed procedure, its purpose, the risks involved, and the alternatives to performing the procedure.† The Court stated:

> In sum, the patient's right of self decision is the measure of the physician's duty to reveal. That right can be effectively exercised only if the patient possesses adequate information to enable an intelligent choice. The scope of the physician's communications to the patient, then, must be measured by the patient's need, and that need is whatever information is material to the decision. Thus the test for determining whether a potential peril must be divulged is its materiality to the patient's decision. (8 Cal. 3d at 245.)

The Court recognized that the scope of disclosure defied simple definition and found that there were at least two applicable limitations. First, no long discourse was necessary about all the possible complications which might occur. The Court felt that a patient was principally concerned with those complications involving risk of serious injury or death and those relating to re-

*A general review and analysis of informed consent was prepared for the American Medical Association Office of the General Counsel and appeared in a series of law and medicine notes in JAMA as follows: Holder AR: Informed consent—Its evolution. JAMA 214:1181-1182, Nov 9 1970; Holder AR: Informed consent—The obligation. JAMA 214:1383-1384, Nov 16, 1970; Holder AR: Informed consent—Limitations. JAMA 214:1611-1612, Nov 23, 1970; Simonaitis JE: Recent decisions on informed consent. JAMA 221:441-442, Jul 24, 1972; Simonaitis JE.: More about informed consent: Part 1. JAMA 224:1831-1832, Jun 25, 1973; Simonaitis JE: More about informed consent: Part 2. JAMA 225:95-96, Jul 2, 1973.

†For mnemonic purposes, disclosure requirements may best be remembered by equating *"nature, purpose, risks* and *alternatives"* with *"no* physician *risks* the *alternatives"* of failing to provide such disclosure.

cuperation. Second, the Court stated that there need not be disclosure of slight risks from common procedures. As an example of a common procedure, the Court referred to the drawing of a blood sample, the risks of which include, among others, septicemia, endocarditis, thrombophlebitis, pulmonary embolism and death. However, not withstanding the seriousness of any of these risks, they are infrequent occurrences, and given the common nature of the procedure involved—that is, drawing blood—none of the foregoing risks need be disclosed.

Even where disclosure is required and none has been given, liability will not automatically attach for the failure to make the necessary disclosure. The Court held that even in these circumstances there is no liability unless it is established that, had the disclosure been made, consent to the proposed procedure would not have been given. The Court stated the patient has the right to testify that had disclosure been made he would not have consented to the procedure. But the Court recognized that a patient who has gone through a stormy recovery or possibly suffered permanent disability may not be completely free from prejudice. Accordingly, the Court determined that the test of liability will depend not upon the patient's analysis of whether he would have consented but upon whether a prudent person in the patient's position, when fully informed, would have consented to the procedure. If such a prudent person when fully informed would have consented, then no liability attaches. If such a prudent person when fully informed would not have consented, then liability will attach.

Even where no disclosures are made, the Court determined there were two defenses to liability. First, if the patient requests that no disclosure be made, then none is required and no liability will attach for not having provided the disclosure. Second, if the disclosure would prevent the patient from dispassionately weighing the risks, then no disclosure is required. But as to this latter defense the Court stated the doctor will have to show by a preponderance of the evidence that that was the case. (Notwithstanding the Court's comments, this second defense should never be applicable. Meaningful consent requires full disclosure. If a patient is not competent to receive all the information then he is not competent to give a valid consent. In such circumstances, the consent should be obtained from those who may be legally qualified to consent on his behalf.)

The *Cobbs* decision emphasizes the importance of informed consent in California. The patient must be informed of whatever would be material to his decision, which generally includes the nature of the procedure, its purpose, the risks and the alternatives. It is the patient who has the right to determine whether to have the recommended procedure done. Only the patient, and not his treating doctor, is in a position to evaluate the patient's nonmedical needs, whatever they may be, and to determine on the basis of those needs what should be done to his own body. (The recent trend of informed consent cases emphasizing the patient's rights as exemplified in *Cobbs* has been both praised as vesting the ultimate determination of treatment where it properly belongs—with the patient,[2] and damned as creating a legalistic fiction that destroys good patient care.[3])*

While *Cobbs* is a landmark decision setting forth significant new law, there has been no study quantitating how widely known it is among the California medical community and, if known, what effect if any it has had on procedures for obtaining informed consent. In June 1974 the California Medical Association published a special report on informed consent, in the form of questions and answers, reviewing the major holdings of *Cobbs*.[4] In addition, various committees of the California Medical Association have published position papers for anesthesiologists, family practitioners, neurologists, ophthamologists, orthopedic surgeons, pathologists, pediatricians, urologists, physicians specializing in chest diseases, and physicians specializing in physical medicine and rehabilitation.†

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*For a further analysis of *Cobbs* see Bamberg DF: Informed consent after Cobbs—Has the patient been forgotten? San Diego Law Rev 10:913-927, Jun 1973; Novack BB: Informed consent and the patient's right to "no." Loyola of Los Angeles Law Rev 6:384-397, Jul 1973; Kassenick LW, Mankin PA: Medical malpractice: The right to be informed. Univ. San Francisco Law Rev. 8:261-281, Winter 1973.

†See the following pamphlets: *On the Matter of Informed Consent for the California Anesthesiologist,* California Society of Anesthesiologists and the Scientific Advisory Panel to the Section on Anesthesiology, California Medical Association (CMA); *Informed Consent in Chest Diseases,* CMA Scientific Advisory Panel to the Section on Chest Diseases; *Informed Consent,* Committee Report, CMA Section on General and Family Practice; *On the Subject of Informed Consent for Neurological Procedures,* CMA Scientific Advisory Panel to the Section on Neurology; *Suggested Guidelines for Ophthalmologists re Informed Consent,* CMA Scientific Advisory Panel to the Section on Ophthalmology; *On the Matter of Informed Consent for California Orthopaedic Surgeons,* CMA Scientific Advisory Panel to the Section on Orthopedics; *Informed Consent in Pathology,* CMA Scientific Advisory Panel to the Section on Pathology; *Some Thoughts on Informed Consent in Pediatrics,* CMA Scientific Advisory Panel to the Section on Pediatrics; *Informed Consent in the Specialty of Physical Medicine & Rehabilitation,* CMA Scientific Advisory Panel to the Section on Physical Medicine and Rehabilitaton; and *Informed Consent in Urology,* CMA Scientific Advisory Panel to the Section on Urology. (California Medical Association Scientific Advisory Panels, 731 Market Street, San Francisco, CA 94103.)

There is no question that *Cobbs* has resulted in some changes in obtaining informed consent, which perhaps are best exemplified by changes in consent forms. While it is unknown to what extent consent forms have changed, in some circumstances they have changed from a "blank check" form in which the patient authorizes the doctor to perform a particular procedure and anything else the doctor deems necessary, to a form in which the patient is informed that he has a right to be told of the nature and purpose of the proposed procedure, the risks of complications and the alternative procedures which may be available. (A good example of this latter form is the new model consent form for teaching hospitals prepared by the California Hospital Association, which in relevant part provides as follows: "Doctor _____ has explained to me that these surgical operations and special diagnostic and therapeutic procedures all may involve calculated risks of complications, injury or even death, from both known and unknown causes, and no warranty or guarantee has been made as to result or cure. I recognize that I have a right to be informed of the nature and purpose of the operation or procedures, the risks of complications, and the alternative methods of treatment, if applicable. Further, I recognize that this form is not intended to be a substitute for the explanations of the nature and purpose of the operation or procedures, the risks of complications, and the alternative methods of treatment, if applicable, which are to be provided by the physician mentioned above . . . ."[5])

Under *Cobbs* the adequacy of consent procedures may be analyzed by considering the appropriate use and limitations of consent forms. Consent forms should not be relied upon to provide the disclosures required by *Cobbs*. The problem with consent forms is that they are not particular to an individual patient. While the nature and even the purpose of a particular procedure may be fairly general from patient to patient, the risks and alternatives of a particular procedure will vary from patient to patient depending on the patient's age, his health and the acuteness of his medical problem. Where the nature and the purpose of a particular procedure do not change from patient to patient, then they may adequately be disclosed in a consent form, but generally a particular procedure's risks and alternatives should never be disclosed by use of consent forms. Rather they should be disclosed orally by the treating physician to his patient. An example of this dichotomy is a consent form for an angiogram in which the nature of an angiogram is set forth and then the patient is informed of the estimated complication rates for carotid, brachial and femoral studies; informed of the rates for permanent complications and mortality, and is provided with an overall grave complication rate of permanent paralysis or death. While the statistics on complications may be completely valid and interesting to the medical profession, they are averages and are not particular to an individual patient; they therefore may be misleading as to the risks to the patient whose informed consent is sought.

Although consent forms should not be relied upon to meet the disclosures required by *Cobbs,* they may serve a valuable function if they are used to ensure that those disclosures are made by the treating physician to his patient, that the patient understands those disclosures and that the patient understands that it is solely his discretionary decision as to whether the recommended procedure will be carried out. If consent forms are to serve the function of ensuring informed consent within the meaning of *Cobbs,* they should contain the following provisions: First, "Your consent to any medical procedure is an important decision, as any medical procedure may involve the risks of serious injury or death from known or unknown causes and for which no guarantee may be made." This provision informs the patient that any procedure which will require his consent is serious in nature and must be carefully considered because of the consequences which may occur, and that as to any medical procedure there may be no guarantees of results.* Second, "You have a right to be informed by your doctor of the nature and purpose of the procedure to be performed, the possible complications, and any alternative methods of treatment which may be available, all of which your doctor will explain to you in terms you can understand." This term informs the patient of what he is entitled to know, tends to ensure that he will be provided with all the disclosures required by *Cobbs,* and tends to reduce the likelihood of the patient claiming that he was not so informed. Third, "You are en-

*In one California appellate decision subsequent to *Cobbs,* a patient was informed that the contemplated procedure involved the risk of serious injury or death, but the nature of the possible serious injury was not disclosed. The Court determined in that instance that the disclosure given, while not specifying the type of risks involved, was nonetheless sufficient under *Cobbs. Morgenroth vs Pacific Medical Center, Inc.,* 54 Cal. App. 3d 521, 126 Cal. Rptr. 681, (1st Dist. 1976).

couraged to ask questions about what your doctor tells you." This clause helps insure that the patient will understand what he has been told. Fourth, "Do not sign this consent form unless from what your doctor explains, you have an understanding of what procedure is to be done, the purpose of the procedure, the possible complications, and what alternative procedures may be available, and unless considering your understanding you desire your doctor to perform the procedure." This statement is a further explanation of provisions two and three above, and emphasizes that it is the patient who has the right to determine whether or not the proposed procedure is to be carried out. Fifth, "Even after giving your consent by signing this form, you are free at any time, prior to the performance of the procedure to withdraw your consent." This statement reemphasizes that it is the patient's right to determine whether to have the procedure performed and that that right is a continuing right.

Regardless of whether a consent form is employed, the treating physician should be mindful that there will always be some question as to whether the disclosures were in understandable terms. Under *Cobbs,* it is incumbent upon the treating physician to ensure that the disclosures have been stated in terms understandable to a competent lay person. If the treating physician is to minimize the possibility of any subsequent claim by his patient that there was either a lack of disclosure, or lack of understandable disclosure, then the treating physician's record of his authorization to proceed should not consist solely of his patient's signed consent. Rather in obtaining any consent, the treating physician should record in the patient's chart the disclosures made, and the fact that the patient was given an opportunity to ask questions concerning those disclosures, that the patient acknowledged his understanding of the disclosures, and that in the physician's opinion the patient when consenting was competent to and did understand those disclosures.

The importance of recording the foregoing information in the patient's chart cannot be overemphasized. Following any medical procedure, a patient may not remember what he was informed, whether he had any understanding of what he was told and—if suit is brought—he may well testify that he was never provided with any disclosures. There has been little research done on what a patient remembers of the circumstances of his consent, but there has been at least one reported study.

Drs. George Robinson and Avraham Merav recorded all informed consent conversations with their cardiac surgical patients at Montefiore Hospital and Medical Center in New York for a period beginning in January 1975.[6] The patients were given *Cobbs* type disclosures. Four to six months after operation, 20 patients were randomly selected for repeat interviews to determine their recall of what they had been informed before giving their consent. The patients were graded on a scale from 0 to 100 percent for primary recall (their recall without any suggestion of what they had been informed), and 0 to 100 percent on their secondary recall (what they could remember with suggestion of what they had been told). The findings were reported at the Twelfth Annual Meeting of the Society for Thoracic Surgeons in January 1976.

Drs. Robinson and Merav found that there was poor retention in all categories of disclosure. The poorest retention was on potential complications, for which there was 10 percent primary recall and 23 percent secondary recall. In other words, the 20 patients reinterviewed on the average could remember only 10 percent of what they were told about potential complications, without suggestion of what they had been told. They could remember only 23 percent of what they had been told about potential complications, with suggestion of what had been said. For the 20 patients for all categories of information, 17 scored 50 percent or less on primary recall, and 12 scored 50 percent or less on secondary recall. The patients' average recall of information was 29 percent primary recall, and 42 percent secondary recall. Sixteen of the 20 patients denied that certain major items of disclosure were discussed at all, and 13 of these 16 denied having been informed on multiple significant items of information. Moreover, Drs. Robinson and Merav found that beyond the failure to recall, or even a denial that certain information had been conveyed, there was also in 13 of the 20 patients a significant degree of fabrication of information which supposedly had been conveyed, but which had never been conveyed. The obvious conclusion is that a doctor should not rely on his patient's memory as to informed consent.

In summary, the concept of informed consent is of increasing significance in California. The

concept involves a legal obligation imposed on a treating physician in obtaining his patient's consent, to disclose to the patient whatever information would be material to the patient's decision, including the nature and purpose of the procedure, and the risks and alternatives to the procedure. The disclosures should be made orally by the physician to his patient, and not through the use of consent forms which are not particular to individual patients. Consent forms may be of significant value if employed to inform the patient of his right to disclosures, thereby helping to ensure that the disclosures will be made and that the patient will not contend otherwise. To further ensure that the obligation has been met, and to further minimize the possibility of any subsequent contention that it was not met, the treating physician should record in the patient's chart the circumstances of the patient's consent, and should not rely on the patient's unreliable ability to recall those circumstances. Any failure by the treating physician to make the necessary disclosures exposes him to liability to his patient even though he was not negligent in the treatment of the patient.

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SKIN CANCER SURVEY

A one-year survey of nonmelanotic skin cancer in the United States is being undertaken by the National Cancer Institute and the United States Environmental Protection Agency in seven areas of the country. The survey will cover the areas of Atlanta, Detroit, New Orleans and Seattle, the San Francisco Bay area and the entire states of New Mexico and Utah. The survey has the approval of the American Academy of Dermatology.

There is growing concern regarding the possible increase in skin cancer as a result of the depletion of the ozone layer by supersonic aircraft and the use of aerosols. Increased ultraviolet radiation at the ground, apart from its effects on human beings, may affect plant and other animal life in ways that are only beginning to be understood.

Similar data on skin cancer were obtained in 1971-72 by the National Cancer Institute as part of the Third National Cancer Survey. The data have been very useful in relating the incidence of nonmelanotic skin cancer to varying degrees of ultraviolet exposure. The present survey will cover the period June 1977 through May 1978.

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Communicating With Hearing-Impaired Patients

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One aspect of establishing effective communication between physicians and patients has not received adequate attention: the special needs and challenges presented by patients with impaired hearing. In this article the term "hearing impaired" is generic and is applied to both those persons who are commonly labeled "deaf" and those labeled "hard of hearing" as a result of a bilateral hearing loss. The general skills, both verbal and nonverbal, that a physician must have in order to communicate successfully with a hearing-impaired patient are in essence the same as those required for a hearing patient. Where the divergence occurs is not in the basic skills (empathy, probing and the like) but rather in the means of applying them. Communicating with a hearing-impaired patient makes the use of some combination of the following necessary: speech, hearing, speechreading (lipreading), writing, visual aids, visual language systems and the assistance of an interpreter.

PERSONS WHOSE HEARING has become impaired after the age of approximately 12 or 13 will probably be able to speak very intelligibly. The structure of their verbal production often will be no different than that of a person whose hearing is good. It is likely, however, that there will be some aberrance in voicing, and in the articulation of some vowels and consonants. The degree of this aberration will depend on the degree of loss, the person's training and other individual factors.

In those who have had a hearing loss before the age of approximately 12 or 13, there will be distortion of speech pattern, intonation and syntactic structure—to the point that most persons with a severe or profound loss that occurred before the age of 5 or 6 will have speech that is either totally incomprehensible or understandable only by those with a good deal of experience interpreting "deaf speech." With such patients a physician must rely on visual means of communication: writing, speechreading, visual media (charts, diagrams and the like), finger spelling and signing (visible, conceptual symbols, produced with the hands, face and body). For many in this group of patients a trained interpreter will be necessary for any communication between physician and patient to occur.

Hearing

In general, it is better to assume that spoken communication alone will be insufficient, leaving it to the hearing-impaired patient to correct you if you are wrong. This information itself is not always easily obtained, as many hearing-impaired people, out of pride or habit, will smile and nod

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as you question them and present information, when in fact they do not follow you at all or at least not completely. The smile and nod syndrome is noticeable in any situation where one language group meets another at different levels of common linguistic understanding, but with a hearing-impaired person working with a doctor, the clear communication of ideas on both sides must be constantly probed and refined for obvious reasons.

Many hearing-impaired people use hearing aids with varying degrees of benefit. For some, amplification allows them to function with little loss of auditory input. Others regain access to only part of the language-relevant auditory input and, for still another group, a hearing aid provides only cues to gross environmental noise. In this latter group, little or no linguistically useful information is received.

Speechreading

Many hearing-impaired persons will be good speechreaders. One must realize, however, that for standard English only about 30 percent of the speech sounds, or phonemes, are visible on the lips under ideal conditions.[1] Assuming no linguistically useful residual hearing, the rest of the information must be filled in by speechreaders based on their knowledge of standard English structure, on their knowledge of the topic being discussed and on their general level of verbal sophistication. As a result of these differences and an elusive talent variable, persons with the same degree of loss will vary tremendously in their ability to receive communication through speechreading alone.

Through a combination of speechreading and amplification, some persons will be able to combine the auditory and visual cues successfully enough to carry on a conversation with only occasional problems. However, as noted before, for many persons no linguistic gain can be noted and a hearing aid serves only to maintain an awareness of environmental noise.

The use of medical terminology or other specialized language is a special problem for hearing-impaired patients. All speechreaders must rely heavily on their previous experience with the vocabulary and topic at hand. Any massive influx of new vocabulary will greatly impede their ability to follow a speaker. For those who operate at the lower levels of speechreading skill, the problem becomes greatly magnified. Obviously, a physician must be ready to convey ideas at varying levels of vocabulary difficulty.

Writing

Probably the first communication alternative that a physician might think of using when normal conversation is blocked is the use of writing. Writing can be used successfully with some hearing-impaired patients, especially when used in combination with understandable or partly understandable patient speech and good speechreading by the patient of the doctor's speech.

Two factors must be considered before you decide to rely on writing as a supplementary mode or as the sole mode of communication. The first of these is the restrictive nature of writing. It is slow, ponderous and frustrating to use as a conversational mode. Try carrying on a general conversation in writing with a hearing friend for half an hour or 45 minutes—then do the same thing on a technical topic about which only one of you is knowledgeable.

A second consideration is the patient's knowledge and understanding of standard English. In the deaf community, the terms "high verbal" and "low verbal" are frequently used to describe a hearing-impaired person's knowledge of and ability to communicate in standard English. A high verbal person is one who has very good to perfect mastery of standard English structure, a large vocabulary and generally high levels of traditional verbal abilities. These persons may or may not have speech upon which you can rely, but they can produce and read written standard English very well. The low verbal members of the community will have varying degrees of mastery of standard English. The sentences they write will be simple and are likely to include grammatical structure which is unlike standard English. These persons have as their primary linguistic mode, Ameslan (American Sign Language), which is grammatically distinct from standard English. They will produce written information which you may or may not be able to use as an information source.

Further, they will have great difficulty following your ideas if you use complex sentences or vocabulary. For the latter group, then, it is very likely that you will need an interpreter. For the former, it will depend partially on your patient's preference and partially on your judgment as to the success of your communication.

Visual Aids

The worn adage "a picture is worth a thousand words" is never truer than in work with hearing-impaired people. Any chart, diagram or picture that can be used to illustrate medical terminology or processes will be of great benefit to physician, patient and interpreter. Needless to say, the visual aids developed for such use would probably be of great value to many hearing patients.

Visual Language

Visual language takes a variety of forms in the hearing-impaired community. The decision as to whether it is necessary to include it in your relationship depends upon one factor. If a patient depends upon some form of visual language outside of your office, then he or she will need it inside your office. The form chosen will vary, but it probably will include some combination of the following:

Finger Spelling

In the American system of finger spelling, the preferred hand is used to spell out each word to be communicated. Each letter of the alphabet has a different hand configuration, and with experts, communication can be fairly rapid, though considerably slower than the spoken communication to which those with good hearing are accustomed. Though some persons have been trained and will continue to use finger spelling exclusively, most will use finger spelling only for those words, concepts and technical jargon for which no sign is available. With an expert using finger spelling at full speed, it is doubtful that an untrained observer could even begin to see the forms of letters at first. Reception involves specific perceptual and cognitive learning, as does any other form of linguistic communication. However, any physician who can finger spell and read finger spelling—even badly—tremendously facilitates his relationship with deaf patients. First, as with any linguistic group, the very fact that someone is willing to try to communicate in their language means a great deal to the hearing-impaired person. Patients will feel that such a physician is more likely to accept them, that he or she cares about them and in turn, they will be more likely to accept and trust the physician sooner. Hearing-impaired persons have suffered and continue to suffer a great deal of prejudice socially, vocationally and economically—not unlike that suffered by racial and ethnic minorities. As a result, for those whose identity is closely tied to the deaf community, there is a good deal of underlying mistrust and hostility toward the hearing world. This is often an important and sometimes difficult obstacle for a physician to overcome.

In an emergency situation, moreover, it is quite possible that the ability of a doctor to read and produce finger spelling—even slowly—could be a comforting, it not a lifesaving factor.

Signs

For vocabulary and concepts in general situations, a system of conceptual signs has been developed. The sign is a configuration of the body which stands for a concept or word, alleviating the need to use finger spelling for everything and making rapid conversation possible. The system of signs is growing rapidly to include more vocabulary. Fluent users frequently generate new signs which are specific to their needs in their own jobs and lives.

Whereas in standard English nuances of meaning are often communicated with the use of totally different words, in using these conceptional signs the nuance is often expressed by the use of the same basic sign with the addition of a change in other parts of the body, such as facial expression, or with variation in the way the sign is produced (made very large, very small, very slowly, rapidly or vehemently, and the like). The boundaries between signing, mime and drama disappear for a fluent user of sign. As a communication medium, signing is rich, exciting and dramatic, serving hearing-impaired people as well as the spoken language serves those who hear.

Given the two modes discussed, finger spelling and signing, two general systems of communication are then used.

Ameslan

Ameslan, or American Sign Language, is the "native language" of most persons who identify themselves with the hearing-impaired community. Some learn it when they reject the hearing world or accept their deafness as adolescents or adults; others acquire it from parents, peers, or teachers in childhood. It is grammatically distinct from standard English. High verbal users of Ameslan will use signing, mime and finger spelling, where necessary, to carry on their daily lives. Low verbal users tend to rely more on signing and mime and less on finger spelling.

Manual or Signed English

In schools for deaf persons where standard English is taught and used, a second general form of sign language has developed. Signs drawn from Ameslan and finger spelling are integrated with the grammatical structure of standard English. Standard English word order, syntactic markers (*s, 's, n't,* for example), articles (*a, an, the*) and the like are added. In so doing, a bridge between visual language and standard English is provided which aids in the development of bilingual persons—people who can potentially operate well in both a standard English dominated society and in the hearing-impaired community. These "anglicized" forms of sign language are considerably slower and more tedious to use, if taken to the extreme, than is Ameslan. As a result, a high verbal hearing-impaired person who lives in both worlds will generally adjust his or her communication system to the audience. Among friends and family the communication tends toward heavier use of Ameslan. Among outsiders of various types, the communication is more carefully structured along standard English lines. While this bilingualism is the ideal, for many it is unattainable and it is the low verbal, exclusive Ameslan user with whom the physician will face the greatest challenge, even with the use of a highly skilled interpreter.

The Interpreter—Role and Function

An interpreter becomes a necessity as an interface between the hearing and the hearing-impaired in two basic situations:

- When one-to-one communication is impossible because of some combination of the factors discussed earlier,
- When the absolute importance of the communication (such as discussing a major surgical operation) or the imposition of time strictures leaves no room for slow or occasionally inaccurate communication.

In such cases, even a high verbal hearing-impaired person will often prefer the use of an intermediary. The interpreter's role then is to become the interface between the two primary participants, to rapidly and accurately transmit information and ideas from the hearing-impaired to the hearing and back again. Depending on the nature of the conversation and upon the degree of the match of the two persons' verbal abilities, the interpreter must choose between two additional functions—that of translating and that of interpreting. Translating involves the verbatim tranference of each participant's production, word for word. Both content and form, then, are held constant. This one-for-one transference is most easily attained between two persons who could be labeled high verbal.

Interpretation becomes necessary when there is likely to be a mismatch in the verbal abilities, vocabularies, and so forth, between the doctor and patient. In such a case if an interpreter directly translates a doctor's phrasing and words, the patient would be no better off. He or she could not understand the meaning of what was being said even though it was being transformed into visual language. Interpretation then involves keeping the ideas and concepts being communicated equivalent, while varying the absolute structure and vocabulary, so that both parties can understand what is being said. Consequently, an interpreter's task is not an easy one, and should not be undertaken in crucial situations except by highly skilled and trained interpreters. The use of friends or family members as interpreters should be avoided, especially when the possibility of discussion of sensitive information and the importance of confidentiality are considered.

The National Registry of Interpreters for the Deaf (NRID)* is an organization to which you or your patient may turn for selection of an appropriate interpreter. It is an organization that has developed rigid guidelines and certification procedures for those who wish to become interpreters and it can provide you with the names of certified interpreters in your area.

General Suggestions

In the initial contacts with a deaf patient, one should emphasize both the confidential nature of your conversations and your willingness to be stopped if you have said something that is unclear or if you are doing something that interferes with speech reading. During your interviews, you will need to probe carefully the patient's understanding of what you have said and be prepared to provide explanations of medical jargon in lay terms, should the terminology be new to the patient. In addition, sudden or unannounced shifts in topic can be very confusing and will often cause a breakdown in communication. Be sure

*Further information can be obtained by writing the National Registry of Interpreters for the Deaf, Post Office Box 1339, Washington, D.C., 20013.

to tell the patient that you are going to change topics and what you will be talking about.

Maintaining constant eye contact with patients is crucial, as they will tend to follow your glance around the room, expecting that someone has entered the room or that something is happening in another part of the room; on the other hand, they may assume that you are uncomfortable with them, bored or otherwise disinterested. They will watch your nonverbal behavior carefully for signs of shock, dismay or frustration. If you experience these, or other strong feelings, it is best to share these with deaf patients so as to expand the relationship rather than destroy it. It is also possible that anxiety may cause them to misinterpret your nonverbal behavior and become unnecessarily hurt, insulted or confused. It is important, therefore, that you watch their nonverbal behavior for cues of confusion or distress, and when you see such cues, investigate the source with them immediately.

Tips That Will Aid Speechreading

Keep a distance of between 3 and 8 feet between you and the patient and make sure that the lighting is good. Excessive brightness or heavy shadows on your face will interfere with speechreading, as will a strong light source coming from behind you (such as a window). In case of the latter, close the drapes or move your chair in front of a neutral surface.

Avoid odd lipstick configurations or heavy beards and moustaches which distort or hide your mouth. Always look directly at patients so they can see you full face; avoid glancing or wandering around the room, digging in files or blocking the patient's view of your face and mouth with your hands or other objects. It is best to speak at a normal conversational rate and in a normal conversational tone—unusual variance in either will so distort your speech patterns that speechreading will become difficult, if not impossible. Finally, be aware that loud speech can be painful to the wearer of a hearing aid and will not get additional sound through to a profoundly deaf person.

Tips On The Use Of Visual Materials

Visual aids can provide an extremely valuable source of information when used effectively. To this end, such aids should be propped up so that they are vertical and as close to you as possible without blocking your face. In this way a patient can see both you and the aid simultaneously, thereby avoiding having to constantly shift visual focus. Become skilled at working with a visual aid from behind so that you can point things out without changing the aid's position or your posture constantly.

Since the patient can look at only one thing at a time, do not talk about a visual aid and point to its intricacies simultaneously. Shift back and forth as the patient shows or communicates readiness to do so. Finally, it can be very helpful to have a bibliography of materials, to which you can refer patients if they wish to read more about something you have discussed.

Tips On The Use Of An Interpreter

It is preferable when choosing an interpreter to select one who is certified by the National Registry of Interpreters for the Deaf. Once the three of you are together (you, the patient and the interpreter) be sure to seat the interpreter as close as possible to you so that the patient avoids the "ping-pong" effect (excessive movement of the eyes between you and the interpreter). Emphasize to the interpreter your desire to be told if miscommunication is occurring somewhere or if time is needed to catch up or reexplain something, or for a brief break. It will greatly help an interpreter if you monitor him or her with your side vision. This allows you to develop the ability to tell how well the interpreter is keeping up with you and thereby to pause when he or she falls behind. In regard to your role, always talk directly to the patient and avoid talking about a patient in the third person. For example, avoid phraseology such as, "Tell her _____," or "Ask him _____." Finally, do not assume that you can relax your efforts to communicate if you have an interpreter. A trained interpreter will automatically avoid many of the pitfalls described earlier—an untrained or poorly trained one may not. Regardless, you must take an active role and keep track of what is going on.

It is hoped that the foregoing material will heighten your awareness and provide you with some strategies to increase your effectiveness in working with hearing-impaired patients. It will take time and practice for you to comfortably put these suggestions into operation—but it should be time well spent as reflected in both personal satisfaction and improved patient service.

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Refer to: Goodman SJ, Cahan L, Chow AW: Subgaleal abscess—A preventable complication of scalp trauma (Medical Information). West J Med 127:169-172, Aug 1977

Medical Information

Subgaleal Abscess

A Preventable Complication of Scalp Trauma

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THE DIAGNOSIS AND TREATMENT of subgaleal abscess is most often self-evident and straightforward. However, these lesions frequently are associated with extended morbidity, and the diagnosis may not be initially obvious. Furthermore, such abscesses are often related to physician errors of omission or commission, and are frequently preventable. Our recent experience with five such cases within a short interval suggests that this complication is not at all uncommon. Our inability to uncover published information regarding clinical, bacteriological and therapeutic aspects of this entity in the English language literature prompted the present communication.

Reports of Cases

CASE 1. A 32-year-old woman was involved in a motorcycle accident and was brought to the emergency room with several parietal and occipital scalp lacerations penetrating to the periosteum. She was lethargic; the neurologic examination gave findings consistent with left frontoparietal contusion. The scalp lacerations were closed in single-layer fashion with 3-0 nylon, and the patient was admitted on the neurosurgery service. The patient became more alert and lateralizing signs disappeared over five days. On the sixth hospital day a subgaleal abscess was noted beneath one of the repaired scalp lacerations. The patient was afebrile. The abscess was opened, draining foul-smelling purulent pus. Staphylococcus aureus, Peptococcus asaccharolyticus and Peptostreptococcus anaerobius were isolated. The patient was treated with local wound care, methicillin and metronidazole. One month of continuous wound care elapsed before epithelialization and complete healing of the 4 by 5 cm defect occurred.

Comment

This patient had multiple superficial lacerations and appeared to have been casual in her personal hygiene. In the emergency room, her scalp was not adequately prepared. Too small an area was shaved and too little time was spent in wound irrigation. The resulting prolonged wound morbidity may have been prevented by initial proper scalp care.

CASE 2. A 31-year-old man was involved in an auto accident and sustained a 4 cm stellate right frontal scalp laceration, several abrasions and lacerations over the chest and hands, and an L1 compression fracture. Neurological examination showed no abnormalities. The scalp laceration was closed in the emergency room in single-layer fashion. On the fourth hospital day, fluctuance and tenderness developed beneath the scalp laceration and rapidly spread circumferentially involving the eyelid. His temperature, taken rectally, rose to 39.2°C (102.6°F). The subgaleal abscess was opened and nonodorous seropurulent fluid drained. Two drains were placed into the subgaleal space through stab wounds. The incision wound was loosely closed with wire. Beta-hemolytic Group A Streptococcus and S. aureus were isolated. Treatment consisted of parenterally given penicillin and methicillin, and local subgaleal irrigation with bacitracin (50,000 units per liter of saline). The drains were pulled on the sixth day, the sutures removed on the eighth day and the wound healed uneventfully.

Comment

When the subgaleal abscess was opened and drained, several in-driven hairs were seen on the periosteum. This abscess may have been prevented by adequate initial wound cleansing.

CASE 3. A 5-day-old infant was admitted after pus drained spontaneously from a large, tense subgaleal abscess. Before vaginal delivery, maternal membranes had been artificially ruptured because of prolonged labor. A fetal electrocardiographic monitor consisting of an insulated electrode with a bared corkscrew end hooked into the scalp of the presenting fetal head had been used for one hour during the final stages of labor. A hexachloro-

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phene bath followed by a providone-iodine shampoo (the routine scalp care applied after such fetal monitoring) was administered. The baby was discharged on the third day with a soft right occipital fluctuance thought to be edema. The mother observed a rapid increase in local heat and swelling, and finally pus spontaneously drained through a thinned out portion of the involved scalp. On examination the child was afebrile and normal except for a large 8 by 6 cm inflamed, right occipital-parietal fluctuant mass with purulent drainage through a more anterior scalp defect. X-ray studies of the skull showed no abnormalities. Blood, wound and cerebrospinal fluid (CSF) was cultured. In the operating room, the subgaleal abscess was treated by incision, drainage and the placement of subgaleal catheters. Wound culture yielded alpha-hemolytic Streptococcus, not group A or D, and Veillonella parvula. Cultures of blood and cerebrospinal fluid were sterile. Methicillin was administered parenterally, followed by orally given penicillin, and the subgaleal space was irrigated with bacitracin solution. The wound healed uneventfully.

Comment

The subgaleal abscess in contrast to scalp infection is an unusual complication of fetal monitoring. In this patient, the subgaleal space was inoculated by the electrocardiographic corkscrew lead, which was inadvertently inserted too deeply into the scalp.

CASE 4. A 70-year-old man sustained a left posterior parietal scalp laceration in a fall. The wound was cleansed, irrigated and closed in a single-layer with nylon. He returned three days later with purulent drainage from the scalp wound which was cleansed and left open. Orally taken penicillin was prescribed and the patient was discharged. He returned seven days later with an extensive 10 by 12 cm necrotizing subgaleal infection. In the center of the wound, there was exposed shiny white bone over a 2 by 3 cm area. Culture showed S. aureus and beta-hemolytic Streptococcus. The scalp was undermined to gain mobility, thoroughly cleansed and irrigated, and the wound edges were approximated after placing four subgaleal drains. Methicillin was given intravenously and subgaleal irrigation with bacitracin carried out. The purulent process subsided but the central portion of the scalp closure became devitalized, exposing a 6 by 6 cm area of white shiny bone. Vigorous local wound care failed to encourage granulation tissue formation to cover the exposed cranium. Two weeks later, a grid of twist drill holes approximately 5 mm apart was placed through the exposed bone down to dura, and over the following three weeks, granulation tissue grew up through the twist drill holes and gradually covered the denuded bone. One more scalp revision was done, and the scalp wound healed approximately three months after the initial laceration.

Comment

A necrotizing subgaleal abscess left the calvarium denuded of periosteum. Frequent interval x-ray studies of the skull failed to show frank osteomyelitis, and eventually the bone was covered by granulation tissue and scalp. The intensity of this closed space infection would undoubtedly have been minimized if the wound had been adequately treated when the patient first returned with purulent drainage three days after the laceration repair.

CASE 5. A 17-year-old man was found unconscious, apparently having fallen backwards. There was an occipital scalp laceration overlying a simple linear fracture. The patient was lethargic and had mild retrograde and antegrade amnesia; there were no other abnormalities noted. The scalp laceration was cleansed, closed in a single layer, and the patient was transferred to Harbor General Hospital because of suspicion of a seizure disorder. The lethargy and amnesia rapidly cleared. Electroencephalogram, brain scan and carotid angiography all gave normal findings. The patient complained of a stiff neck which was attributed to his fall. A lumbar puncture, however, showed an opening pressure of 265 mm of water, 8,250 red blood cells per ml and 10 leukocytes per ml (six lymphocytes and four polymorphonuclear cells), protein level of 30 mg per 100 ml and glucose value of 80 mg per 100 ml. Cultures of cerebrospinal fluid were sterile. These findings were interpreted as being consistent with posttraumatic subarachnoid hemorrhage, and the patient was discharged eight days after the fall.

The patient was readmitted to the hospital two days later. His mother had witnessed several episodes of seizure-like activity. He was febrile (38.6°C [101.6°F] rectally) and had definite neck stiffness. The remainder of the neurologic examination was entirely normal. Meningitis was suspected. Cerebrospinal fluid examination showed normal pressure with crystal clear fluid, four leukocytes per

ml (three polymorphs and one lymphocyte), 60 red blood cells per ml, protein level of 80 mg per 100 ml, glucose value of 73 mg per 100 ml (serum glucose, 102 mg per 100 ml). Gram stain, india ink preparation and cultures of the cerebrospinal fluid were all negative. Re-exploration of the occipital laceration site showed there to be a small subgaleal abscess approximately 4 cm in diameter, spontaneously exuding scanty purulent material. The wound was opened and drained. Culture revealed S. aureus. The patient was vigorously treated with local wound care and intravenous cephalothin. The fever and stiff neck rapidly resolved and the wound healed by secondary intention.

Comment

This patient had a parameningeal reaction manifested by fever and a stiff neck. The source of this reaction was a small subgaleal abscess not initially recognized because of the patient's long hair and an associated incomplete physical examination. This subgaleal abscess collected beneath a scalp laceration, and because of an underlying linear fracture produced inflammatory meningeal signs and symptoms. Consequently, there was a direct route for the potential development of an epidural or intradural suppurative complication.

Discussion

A cursory treatment of scalp trauma invites complications. Reviewing his World War I experiences, Cushing cautioned ". . . even among the walking wounded every scalp wound must be regarded as a potential penetrating lesion of the brain . . ."[1] Botterell and Jefferson warned, "We have come to learn that many of the more virulent organisms do not enter with the missile but are introduced into the wound when it is being dressed . . . . The reassuring words of the doctor or nurse bending over the open wound may carry in the streptococcus."[2]

Although subgaleal abscess may result from hematogenous infection or contiguous spread from calvarial osteomyelitis, the most common cause is direct inoculation of microbes into the subgaleal space following scalp trauma (laceration, or puncture wounds). Once the subgaleal area is infected, inflammation spreads rapidly within the large closed space, threatening the viability of scalp and bone. Intracranial suppuration may result from secondary infection through emissary veins, calvarial foramina, fracture lines or surgical openings in the bone.

Scalp lacerations are frequently repaired in emergency rooms by physicians with varied backgrounds and training. The most basic principles of management are often ignored. The scalp must be examined, retracting hair sufficiently under a bright light to insure thorough inspection. Generous amounts of hair must be shaved when a scalp laceration is identified as extending through galea. Copious irrigation and meticulous cleansing of the wound and adjacent subgaleal space should be done. Wound closure should be done under sterile conditions with particular attention paid to galeal approximation. A sterile occlusive dressing should be applied for at least 72 hours to prevent contamination of the subgaleal space after wound closure is completed. The significance of purulent drainage from a repaired laceration must be stressed in order that extensive subgaleal spread of infection may be prevented by early treatment.

Our preferred treatment of subgaleal abscess is surgical incision with meticulous debridement and vigorous cleansing of the subgaleal space. We leave in several subgaleal drains for twice daily irrigation over four to six days. The wound is loosely closed, permitting much quicker healing per primum compared with the delayed healing by secondary closure. Appropriate antibiotic therapy is administered systemically for one week and

TABLE 1.—*Bacteriology of Subgaleal Abscess Following Scalp Laceration*

	Isolates		
Case No.	*Aerobes*	*Anaerobes*	*Antibiotic(s) of Choice*
1	Staphylococcus aureus	Peptococcus asaccharolyticus Peptostreptococcus anerobius	Methicillin and penicillin
2	Staphylococcus aureus Streptococcus, Group A	. . . .	Methicillin and penicillin
3	Streptococcus, not Group A or D	Veillonella parvula	Penicillin
4	Staphylococcus aureus Streptococcus, B hemolytic	. . . .	Methicillin and penicillin Methicillin
5	Staphylococcus aureus		

orally for an additional week. Complicated wounds involving devitalized scalp or bone will obviously require extraordinary treatment regimens.

The bacteriology of subgaleal abscess has not been previously reported, and our experience has included recently developed anaerobic culture techniques. We observed that four of five cases involved polymicrobial pathogens (Table 1). S. aureus was isolated in four cases, Streptococcus in three and anaerobic cocci in two cases. Therefore, combined therapy of methicillin and penicillin appears to be the treatment of choice. In patients allergic to penicillin, clindamycin or cephalothin is an excellent alternative since they are effective against S. aureus and Streptococcus, as well as anaerobic cocci.[3-5] The polymicrobial cause of subgaleal abscess supports the notion that bacterial synergism may be an important factor in the pathogenesis of serious soft tissue infections, and reaffirms the importance of early surgical intervention in these cases.[6-9]

Infection restricted to the scalp has been reported as a rare complication of fetal scalp monitoring (electrocardiographic) and blood sampling.[10,11] Such infections have usually been diagnosed at 4 or 5 days of age, and many of the cases were reportedly "sterile" on routine culture. Sophisticated anaerobic culture techniques were not employed in these studies. We do not know of a previous report of a subgaleal abscess complicating fetal scalp monitoring.

Meticulous attention to fundamental principles of surgical management remains the single most important factor in reducing the incidence and morbidity of subgaleal abscess complicating scalp wounds.

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Medical Information

Barium Peritonitis

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BARIUM MEAL (upper gastrointestinal) and barium enema studies have long been considered essential procedures for evaluating diseases of the gastrointestinal tract. While it is generally accepted that these procedures are safe and morbidity is low, unfortunately such procedures are not entirely innocuous and serious complications have been reported, including necrotizing proctitis,[1] peritonitis,[2] barium granuloma of the rectum,[3] septicemia,[4] embolization[5] and fatal intravasation.[6]

Between March 1974 and October 1975 three cases of barium peritonitis occurred in our hospital from perforation of the gastrointestinal tract during routine barium meal or barium enema examinations. In one patient there was extravasation through a normal cecum and hypovolemic shock developed while he was still on the x-ray table. In another patient, who had a gastric outlet obstruction, an anterior gastric ulcer perforated 72 hours after an upper gastrointestinal study. In a third patient, a normal rectum perforated and symptoms of peritonitis developed six hours after a barium enema procedure. The patients with the cecal and the gastric perforations were treated with aggressive fluid resuscitation; immediate surgical resection of the site of perforation; removal of the barium, feces or other foreign bodies, and peritoneal lavage with large volumes of physiological saline. The patient with the rectal perforation was treated medically with nasogastric suction, fluid therapy and antibiotics. All three patients survived the described treatment.

Rectal Laceration

Most rectal lacerations occur between 3 and 8 cm from the anal verge on either the anterior or

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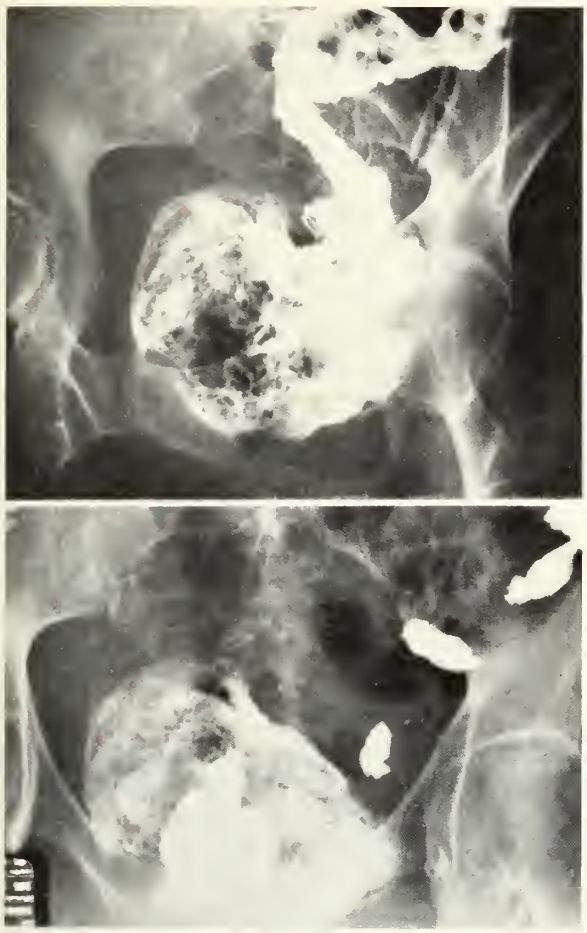

Figure 1.—Top, eight hours after a routine barium enema study. Evidence of barium extravasation from perforated rectum is seen. **Bottom**, 96 hours after barium enema examination. There is an extraluminal extravasation of barium from perforated normal rectum.

posterior wall of the rectum.[3] The causes of these complications include improper placement of the enema tip, overinflated enema balloon, placement of the balloon beyond the distensible area, recent rectal biopsy, excessive intraluminal pressure and preexisting rectal disease.[7-11] Most of the mentioned contributory factors could be reduced if one recognizes that these procedures are not hazard free. Rectal biopsy should be deferred until after a barium enema examination. The balloon should never be placed beyond the distensible rectal area and should not be distended more than necessary to obtain the proper examination.

Fortunately, the most frequently reported cases of barium extravasation occurred in the rectal and sigmoid colon. In most of the cases, the contrast medium was confined below the peritoneal refluxtion. In our patient, a Bardex® tube was used because of some inability to retain the barium. Six hours after the barium enema procedure, abdominal pain occurred accompanied by urgency and dysuria, and the temperature spiked to 39.6°C (103°F). On rectal and sigmoidoscopic examination, a 2½ cm oval laceration was noted in the anterior surface of the rectum at a 4 cm level from the anal verge. No other pathology was found up to the 20 cm level. Findings on an x-ray study included evidence of a perirectal extraluminal extravasation of barium (Figure 1). The patient was treated medically with nasogastric suction, fluid therapy and antibiotics. After ten days of medical management, the peritonitis subsided and the patient had an uneventful recovery.

Cecal Perforation

Perforation of a normal intraperitoneal colon and cecum, in particular, is most likely due to excessive intraluminal pressure.[9-10] When the colon begins to distend, the radius of the colonic lumen is increased and the law of La Place is invoked. According to this law, the pressure required to stretch the walls of a hollow viscus decreases in inverse proportion to the radius of the cylinder. Applying this law to the colon by giving an equal pressure throughout the colon, the greatest distention will occur in the portion of the colon with the largest radius. Because the cecum has the largest diameter, it is usually the site of rupture. To reduce the incidence of perforation of a normal cecum or right colon, the volume of barium should not exceed 4,500 ml in an average adult. The contrast medium should not be introduced too rapidly to avoid the incidence of sudden bursting pressure from colonic spasm.[10] In the event that a possible distal obstructive lesion is suspected, a water soluble contrast medium should be used in order to minimize the chance of precipitating a bowel obstruction and perforation, and to lessen the severity of peritonitis.[12] When a hyperosmolar water soluble material is used, the patient must be monitored closely for possible fluid and electrolyte imbalance.

In our patient, approximately 5,500 ml of barium was introduced during the barium enema procedure. Suddenly, an acute abdominal pain occurred. Fluoroscopic and x-ray study findings documented that extravasation of barium had occurred in the right side of the colon (Figure 2A). The patient immediately became cold, clammy and hypotensive. Hemoglobin level was 18 gm, while it was only 12 gm three hours before the perforation. He was operated upon less than 30

minutes from the time of perforation. Some 2,000 ml of serosanguineous fluid was present in the peritoneal cavity. The entire peritoneum, including the walls of the stomach, small and large bowels, omentum and mesenteries were notably edematous, hemorrhagic and friable. The right part of the colon was distorted to a pronounced degree by the infiltration of barium, making it impossible to do any lesser procedure other than a right colectomy, which was carried out. Large volumes of barium and feces were removed and the peritoneum was irrigated with copious volumes of normal saline. Some of the barium was firmly adhered to the peritoneal cavity and was impossible to remove. The patient received six liters of Ringer's lactate and three units of plasma by the end of operation (3⅓ hours from the time of perforation). The patient's hemoglobin level was 13 gm, still one gm higher than the level determined just three hours before the perforation. There was no gross pathology that could explain the cause of the perforation. Microscopic examination at the site of perforation failed to show any pathology other than barium infiltrated into the bowel wall. A series of x-ray films of the abdomen taken since the patient's discharge showed residual barium in the peritoneal cavity and the appearance has not changed in 24 months (Figure 2B).

Gastric Perforation

Barium peritonitis resulting from perforation following upper gastrointestinal examination is rare, but has been reported in the literature.[13-15] In our patient and the cases reported in the literature, there was indication that distal obstruction was the contributory factor for precipitating perforation. In our patient approximately 72 hours after the upper gastrointestinal procedure, an acute abdominal pain suddenly developed which quickly became generalized. On an x-ray study of the abdomen, the stomach was seen to be notably distended by residual barium; free air un-

Figure 2.—Left, barium dissected along the entire wall of the right colon and perforated into the peritoneal cavity from a perforated normal cecum during a routine barium enema examination. **Right,** the residual barium in the peritoneal cavity has not changed in 24 months since the perforated normal cecum.

derneath the diaphragm was shown on an x-ray film of the chest (Figure 3). Surgical operation was done less than 1½ hours from the time of perforation; 3,000 ml of serosanguineous fluid mixed with barium was present in the peritoneal cavity. The entire peritoneum was edematous, hemorrhagic and friable. The barium and residual food particles were still leaking into the peritoneal cavity from an anterior perforated gastric ulcer at the antrum of the stomach. There was a second large ulcer at the lesser curvature of the stomach which had perforated into the lesser sac and the capsule of the pancreas. Edema and inflammatory processes from these ulcers had caused a gastric outlet obstruction. A subtotal gastrectomy was done and the patient is doing well 15 months postoperatively.

Discussion

In 1916 Rosenthal[13] reported the first case of barium peritonitis from an acute perforation of a duodenal ulcer immediately after a barium meal study complicated by intestinal obstruction. Since that time, there have been a few scattered reports of this complication, but it seems likely that this event occurs more frequently. In 1952 Zheutlin and co-workers[16] queried 100 teaching hospitals and collected 53 cases of barium extravasation occurring in the distal colon with a mortality rate of 51 percent. Lorinc and Brahme[17] found two perforations of the distal colon in more than 10,000 contrast studies, while Gardiner and Miller[18] reported an incidence of one in every 2,250 examinations. However, the true incidence of this complication is unknown.

Perforation of the gastrointestinal tract during barium examination is a rare but highly lethal complication. In untreated patients, mortality is 100 percent, as shown in laboratory models.[19,20] Even with aggressive surgical and medical management, mortality still exceeded 50 percent in both experimental and clinical experience.[12,16,18,20]

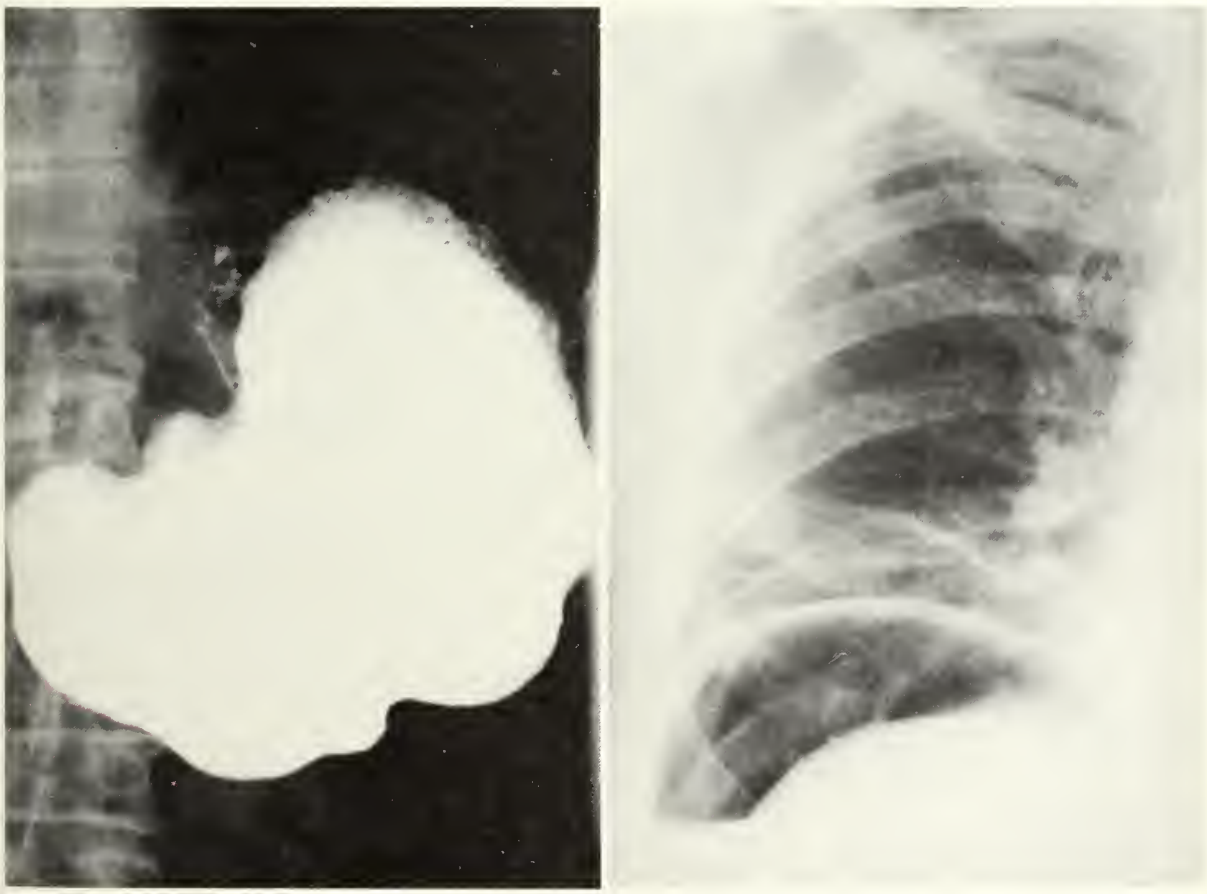

Figure 3.—X-ray films taken at the same time (72 hours after an upper gastrointestinal examination). **Left** shows residual barium in the stomach 72 hours after upper gastrointestinal study. **Right,** free air is seen underneath the diaphragm 72 hours after upper gastrointestinal study and 15 minutes after onset of acute abdominal pain.

Management of this complication should be tailored to the individual patient. Most rectal lacerations where barium extravasates usually are confined below the peritoneal refluxtion which can be safely treated medically with fluid and antibiotics. In perforation occurring above the peritoneal refluxtion with severe peritonitis, surgical intervention should be done as soon as possible after adequate resuscitation because continued spread of barium throughout the peritoneal cavity occurs within time. Increasing the severity of peritonitis by increasing the quantity of barium entering the peritoneal cavity has been documented by Westfall and associates.[20] The barium and other foreign bodies should be removed by irrigation and wiping the serosa with moist laparotomy pads to remove as much as possible. Copious lavage of the peritoneal cavity with physiological saline should also be carried out. The site of the perforation should either be repaired or resected, depending upon the local condition of the bowel wall.

It appears that loss of fluid into the third space is a significant factor in death of patients from barium peritonitis. Therefore, early aggressive intravenous fluid administration should be the mainstay of therapy for treatment of all barium peritonitis. We also recommend early surgical intervention for perforation occurring above the peritoneal refluxtion as soon as the patient's condition stabilizes.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions of general interest are referred to the Scientific Board by the Peer Review Commission of the California Medical Association. Each is sent to members of the appropriate Scientific Advisory Panel.* Their responses are collated, reviewed and then submitted to the Peer Review Commission as the Scientific Board's opinion on the scientific and practice aspects of the question. The Commission adds suggestions to assist peer review units and authorizes publication.*

These opinions and positions are informational only and are not intended to be used as instructions, directives or policy statements. The appropriateness of care in individual cases should not be determined by these answers, but should be reviewed by local peer review committees.

Questions and reprint requests may be submitted to the Medical Practice Questions Committee, Peer Review Commission, California Medical Association, 731 Market Street, San Francisco, CA 94103.

Fundusphoto Camera

QUESTION:

Is the use of a fundusphoto camera considered accepted medical practice for diagnosis and follow-up in diabetic and hypertensive patients? (Asked by Keith E. Vincent, MD, Vallejo, California)

OPINION:

In the opinion of the Advisory Panels on General and Family Practice, Internal Medicine and Ophthalmology, fundus photography can be valuable in the diagnosis and follow-up of patients with diabetic or hypertensive retinopathy. The fundus photos are usually evaluated in conjunction with flourescein angiography. The value of the findings rests on their interpretation by an appropriately trained person, most often an ophthalmologist.

Hysterosalpingography

QUESTION:

What are the medical indications for carrying out hysterosalpingography? (Asked by Blue Shield of California)

OPINION:

In the opinion of the Advisory Panels on Obstetrics/Gynecology and Radiology, the following may be indications for hysterosalpingography: determination of tubal patency, tubal abnormality or abnormality of the uterine cavity; as part of sterility evaluation or after salpingoplasty or premyomectomy or postmyomectomy; to determine intrauterine polyps, endometrial or pelvic masses, incompetent cervix or abdominal pregnancy; to locate a "lost" intrauterine device; to evaluate caesarean section or myomectomy scarring; as part of the diagnostic workup for abnormal uterine bleeding, habitual abortion, repeated pelvic infections, dysmenorrhea, amenorrhea or Asherman's syndrome; to evaluate known renal anomaly or ambiguous external genitalia; or as an adjunct in the diagnosis of unexplained pelvic pain.

Photomotogram (Achilles Reflex Test)

QUESTION:

(1) Is use of a photomotogram (Achilles reflex test) accepted medical practice as an initial test of thyroid function? (2) Is a photomotogram accepted medical practice when used with other thyroid tests? (3) Are periodic photomotograms used to follow the results of therapy accepted practice? (Asked by San Diego Foundation for Medical Care)

OPINION:

In the opinion of the Advisory Panel on Internal Medicine, the photomotogram, while not unacceptable medical practice, has been generally replaced by more sensitive chemical tests. It is no longer widely used as an initial test of thyroid function, or to follow periodically the results of therapy. Panel members felt that use of the photomotogram would be justified in certain circumstances when other tests are not available; and that it may occasionally provide useful information when used in conjunction with other thyroid tests.

*The Scientific Board of the California Medical Association has a Scientific Advisory Panel for each of 23 recognized specialties of medical practice. Each Advisory Panel includes representation from the appropriate department of each of the eight medical schools in California, representatives of specialty societies in the field and representatives from the Specialty Sections of the Association. The Advisory Panels are thus broadly and authoritatively based in both academia and practice.

ARTICLES TO READ IN OTHER JOURNALS

EDITOR'S NOTE: *Members of the Editorial Board on occasion call attention to articles in other journals which they consider to be particularly significant. The editors believe these titles together with a brief assessment of the articles are worth publishing for the information of our readers.*

Idiopathic Pulmonary Fibrosis: Clinical, Histologic, Radiographic, Physiologic, Scintigraphic, Cytologic, and Biochemical Aspects

Crystal RG, Fulmer JD, Roberts WC, et al

Annals of Internal Medicine
85:769-788, Dec 1976

DISCIPLINES: Internal Medicine, Pulmonary Disease

READABILITY: Good

An up-to-date review of this important problem. Pathophysiology is put into perspective with pathology, and newer radiographic techniques. There is an extensive bibliography. A very good review.

—J. DAVID BRISTOW, MD
Seattle

Prevention of Hyaline Membrane Disease with Plasminogen: A Cooperative Study

Ambrus CM, Choi TS, Cunnan E, et al

JAMA
237:1837-1841, Apr 25, 1977

DISCIPLINE: Neonatology

READABILITY: Very good

A cooperative study by the Roswell Park group. They report prevention or amelioration of respiratory distress syndrome through the use of plasminogen. In a controlled experiment involving 400 premature infants, those babies who received plasminogen had one fourth the mortality of the placebo-treated group. One eagerly awaits further confirmation.

—E. R. W. FOX, MD
Coeur d'Alene, ID

The Effect of Fetal Monitoring on the Incidence of Cesarean Section

Hughey MJ, LaPata RE, McElin TW

Obstetrics and Gynecology
49:513-518, May 1977

DISCIPLINE: Obstetrics

READABILITY: Good

A good review of the literature, and of eight years' experience at Evanston Hospital. The authors contend that the pronounced increase in cesarean sections is in part due to the fact that fetal monitoring has given us a new indication for abdominal delivery: fetal intolerance of labor. Furthermore, we have greatly widened our indications for cesarean section: breech presentation in primipara, and "dystocia," which includes uterine inertia, arrest of labor and failure to progress.

—E. R. W. FOX, MD
Coeur d'Alene, ID

Risks to the Offspring of Women Treated with Hydantoin Anticonvulsants, with Emphasis on the Fetal Hydantoin Syndrome.

Hanson JW, Myrianthopoulos NC, Harvey MAS, et al

Journal of Pediatrics
89:662-668, Oct 1976

DISCIPLINES: Neurology, Pediatrics, Obstetrics

READABILITY: Good, concise

An important problem that all physicians caring for women with epilepsy, or their offspring, should know about.

—PHILLIP D. SWANSON, MD
Seattle

Malignant Melanoma: A Review

Kopf AW, Bart RS, Rodriguez-Sains RS

Journal of Dermatological Surgery and Oncology
3:41-125, Jan/Feb 1977

DISCIPLINES: Dermatology, Surgery, Oncology, Pathology, Pediatrics, Radiology, Public Health

READABILITY: Excellent

A beautifully clear, concise and eminently readable monograph on the current status of malignant melanoma in all of its aspects. A monumental work.

—REES B. REES, MD
San Francisco

Complete and up-to-date review of diagnostic and prognostic advances in the field as well as recent developments in treatment.

—RICHARD L. DAKIN, MD
Greenbrae, CA

Contemporary Concepts of Aging: An Overview

Bozetti LP, MacMurray JP

Psychiatric Annals
7:16-46, Mar 1977

Drug Misuse Among the Elderly: A Hidden Menace

Bozetti LP, MacMurray JP

Psychiatric Annals
7:95-107, Mar 1977

DISCIPLINE: Psychiatry

READABILITY: Very good

The entire volume devoted to the elderly discusses their illnesses and problems both physical and psychological, and the interplay between them as well as the ways in which the reactions such patients evoke in those who treat them influence their treatment. The two articles listed are helpful to all who deal with the aged.

—HELEN TAUSEND, MD
Los Angeles

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

STANDARD ORTHOPAEDIC OPERATIONS—A Guide for the Junior Surgeon—John Crawford Adams, MD(Lond), MS(Lond), FRCS (Eng), Consultant Orthopaedic Surgeon, St. Mary's Hospital, London; Civil Consultant in Orthopedic Surgery, Royal Air Force; Production Editor, **Journal of Bone and Joint Surgery.** Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 384 pages, $29.50.

J. Crawford Adams is a well known orthopedist who has previously written outstanding texts for medical students on orthopedics and fractures.

It is not often that a highly experienced and articulate surgeon sets out to describe those operative techniques that have proved successful in his practice. The operative procedures are well detailed by description and simple drawings, but the heart of the text is made up of the "comments" in which he describes the essentials and pitfalls of the procedure and provides a glimpse of his opinions and philosophy. The text is for the most part what the author intends—it is a personal statement, complementary to standard texts and not encyclopedic. It is written primarily for orthopedic registrars or residents and contains a good chapter on surgical approaches and an outstanding chapter on basic orthopedic techniques.

While a surgeon-in-training will benefit from the operative descriptions, this portion of the text will be equally enjoyed by an experienced orthopedist for its clear style, appropriate references and interesting selection of operative procedures.

The appeal of this text will be nearly limited to those working in orthopedics and rehabilitation, although general surgeons may on occasion find it useful.

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FUNDAMENTALS OF ABDOMINAL AND PELVIC ULTRASONOGRAPHY—Volume 6 in the Series: Saunders Monographs in Clinical Radiology. George R. Leopold, MD, Associate Professor of Radiology; Head, Division of Ultrasound, University of California, San Diego, School of Medicine; and W. Michael Asher, MD, & Cdr, MC USN, Division of Ultrasound, Naval Regional Medical Center, San Diego; Clinical Assistant Professor of Radiology, University of California, San Diego, School of Medicine. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1975. 267 pages, with 254 illustrations, $21.50.

The monograph consists of 12 chapters dealing with fundamentals of scanning techniques and anatomic interpretation. The basic physics of ultrasonic wave propagation and image formation has been purposefully excluded from the text.

In addition to an opening chapter dealing with the technique of ultrasound scanning, subsequent chapters contain a specific section on examination methods pertinent to the organ or organ system under discussion. Each chapter then proceeds with a description of the related normal anatomy, followed by well-illustrated descriptions of pathologic processes. Numerous references to potential diagnostic pitfalls constitute one of the text's strongest merits.

The chapters sequentially detail scanning of the liver, gallbladder, pancreas, spleen, urinary tract, retroperitoneum, aorta, pelvis and the gravid uterus. Bistable images form the bulk of the illustrations—as might be anticipated in any work on B-scan ultrasonography written at the time this monograph was assembled. The authors, prospectively recognizing this drawback, have dedicated chapter 11 to gray scale imaging. Unfortunately, though the chapter is admirably written, its scope could not adequately cover the subject in view of what has transpired during the past 18 months in the field of diagnostic ultrasonography. It was the authors' own "inescapable conclusion . . . that gray scale imaging increases the amount of information that can be recorded in scanning." Thus, most of the illustrations do not reflect the optimum in terms of the current state of the art. However, in the opinion of this reviewer, this does not alter the value and pertinence of the authors' descriptions of diagnostic findings based on bistable images.

Real-time scanning, which has been employed for a number of years and which is more recently an important ancillary (sometimes primary) technique in ultrasonic evaluations, is not considered in the monograph.

Three additional attributes are worth considering. The monograph is well organized and easy to read. The authors' own basic research forms the foundation of most of their chapters.

Second, the book contains 12 excellent colorplates of cross-sectional and parasagittal anatomy, with accompanying line drawings and bistable ultrasonograms.

Finally, the last chapter offers 17 case studies with related questions and comments. Both bistable and gray scale illustrations are employed. These cases are carefully prepared and offer a good test of the understanding of the reader.

The illustrations are not sufficiently current and the monograph does not have sufficient depth to serve as a reference text for physicians specialized in diagnostic ultrasonography of the abdomen and pelvis. However, the fine organization, easy readibility, specific references to potential diagnostic pitfalls and well-conceived self-testing chapter make the text worthwhile reading for medical students, technologists, residents or referring physicians interested in obtaining basic information upon which to build.

ROY A. FILLY, MD
San Francisco

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PRINCIPLES OF CLINICAL CARDIOLOGY—An Analytical Approach—Arthur Selzer, MD, Chief of Cardiology and Director of Cardiac Laboratories, Presbyterian Hospital of Pacific Medical Center, San Francisco; Clinical Professor of Medicine, University of California, San Francisco, and Stanford University School of Medicine. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1975. 735 pages, $18.50.

Fact-filled, heavily-referenced cardiology texts presenting multiple viewpoints are common, but a cohesive logical approach to heart disease is a rare textbook finding. Dr. Selzer offers the latter in this text. He presents an appropriate and rational approach to clinical cardiologic problems as his major aim. He is able to put the patient, the results of diagnostic studies and the natural history of various disease entities into appropriate perspective. Recommendations for the optimal management of heart disease result.

The opening chapters explain his approach and his philosophy and the value and vagaries of the history and physical examination are discussed. He reviews the tools available to enhance the diagnostic capabilities of the clinician. In these latter areas, he discusses radiology,

electrocardiography, echocardiography and catheterization with angiography, describing not only their applicability, but on occasion their clear limitations. Each procedure is discussed in terms of the ultimate goal in each patient's care. This section of the text is summarized by an appropriately entitled chapter, "Diagnostic Synthesis," which emphasizes again the need to put all patient data into perspective to allow a reasonable diagnostic yield at an acceptable risk. A section on therapeutics follows. The principles and goals of therapy, rather than many of the particulars are stressed. The remainder of the text offers the more standard review of the major cardiovascular disease entities. It is preceded by a section on the pathophysiology of cardiac lesions in which the author is less concerned with a localized cardiac abnormality than he is with the resultant cardiac performance. The review of major disease entities is not entirely conventional in that the diseases are grouped for discussion to allow their many similarities to be evident. In the discussion of each, the natural history of the disease is emphasized and put into proper perspective with the risk and benefits of diagnostic and therapeutic maneuvers to allow rational management.

The philosophy and goals of the text cannot be faulted. It is refreshing and exciting to think through heart disease and its evaluation with this respected cardiologist. Because of the author's intentions and his approach, however, there are clear limitations to the text. The legitimate controversies raging in many areas of modern cardiology are not often appreciated in this individual approach to cardiac disease. As many of the author's opinions are not supported by factual data in the text, nor in the references, it is often difficult to put his views into proper context. In addition, opinions about a particular approach to specific clinical problems are often scanty and occasionally too general to be clinically useful. The subject matter is specific enough, however, that the book is somewhat advanced for those just beginning clinical cardiology. Thus, there are advantages and disadvantages to this as a major cardiology textbook for readers at any level of experience.

While it is difficult to define the group for whom this book is best suited, the author outlines an approach to cardiac patients which is of value to students and clinicians at all levels. Though his management of some problems may not be universally accepted, it is nevertheless reasonable, consistent, and as valid as many of the alternatives. The text neither aims to be, nor is it, encyclopedic. It occasionally lacks adequate factual data support and specificity of recommendations for a specialist in cardiology dealing with a particular problem. The well taught approach to cardiac problem-solving more than compensates for any lack of minute detail and gives hope that there is, indeed, a way to deal with the complexities of modern cardiology.

JOHN H. McANULTY, MD
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TO YOUR HEALTH—The Pleasures, Problems, and Politics of Alcohol—Richard S. Shore, MD, Assistant Clinical Professor, Department of Psychiatry, University of California, San Francisco, and psychiatrist in private practice, San Francisco; and John M. Luce, MD, Senior Resident in Internal Medicine, University of Colorado Medical Center, Denver. The Seabury Press, 815 Second Ave., New York City (10017), 1976. 230 pages, $12.95.

"I trust in the good sense of the American people that they will not bring upon themselves the curse of excessive use of intoxicating liquors to the detriment of health, morals and social integrity. . . ." With these words Franklin Roosevelt announced the repeal of prohibition. The nature of the lack of "good sense," and other aspects of the history and pharmacology of alcohol are the subject of *To Your Health.*

In early chapters, the authors describe the origins of alcohol and the historical and geographic progression of alcohol use to the American specialty, the highball. In subsequent chapters, the extent of alcoholism with its social and economic implications, the pharmacology of alcohol use and addiction, and the medical complications of alcohol abuse are reviewed. The section on medical management of alcoholism is written for an educated layman, and is too over-simplified to be of use to most medical practitioners.

The two chapters dealing with the disease concept of alcoholism are the most interesting. Acceptance of a disease concept was a critical first step because it moved alcoholics from prisons into various types of treatment facilities. The disease concept has been the foundation for some of the best known and most successful treatment programs, such as Alcoholics Anonymous. But the disease concept is inadequate to explain the complexity of alcohol abuse. Clearly genetics, psychological and social factors, and the pharmacology of the drug alcohol interact in the genesis of problem drinking. Treatment is optimally based on an understanding of how these factors operate in a particular patient. Thus different treatment alternatives—group therapy such as used in Alcoholics Anonymous, individual psychotherapy, psychotropic medications and Antabuse® have proved useful for selected patients. Treatment goals such as complete abstinence or responsible drinking must be developed to meet each patient's needs. The challenge now is to define the characteristics of patients which predict optimal treatment methods and goals. Even the role of physicians in treating problem drinkers, needs to be redefined.

The final chapter, "Dealing With Problem Drinking," is disappointing. Before this chapter, the book flows well and the authors give a balanced picture of the pleasures, problems and politics of alcohol. They carefully constructed a case for treatment programs based on a multifactorial model of alcohol drinking. But in the final chapter the authors offer a number of suggestions, mostly unrelated to previous discussion, which include taxation of alcohol, adding vitamins to alcoholic beverages and changing addiction patterns by modifying laws and health insurance. Some of these are clever suggestions but are disconnected from the major theme of the book. The most important issues are addressed briefly at the end of the chapter. These are education to modify attitudes about alcohol use and development of broad-based treatment programs which include prevention, medical treatment and rehabilitation facilities.

This book by Shore and Luce is a useful and pleasant introduction to the subject of alcohol. It is recommended for professionals in the alcohol treatment field and for educated laymen. It does not offer specific information about managing problem drinkers but does provide a perspective in which to better understand the problems and the treatment alternatives. The book is probably too sophisticated for many problem drinkers themselves, who actually might benefit most from it.

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EXERCISES IN NEUROLOGICAL DIAGNOSIS—Second Edition—John H. Tyrer, MD (Sydney), FRCP(Lond), FRCP(Edin), FRACP, Professor of Medicine, University of Queensland; Senior Neurologist, Royal Brisbane Hospital; Honorary Consulting Physician, Mater Misericordiae Hospital, Brisbane; and John M. Sutherland, MD (Glasgow), FRCP(Edin), FRACP, Senior Neurologist, Royal Brisbane Hospital and Royal Brisbane Children's Hospital; Honorary Reader in Neurology, University of Queensland. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975. 311 pages, $17.50.

This book is designed to be used by medical students, but—I venture to add—could be read with profit by any physician who deals with neurological patients and who wishes to test his clinical acumen on straightforward problems. There are twenty "clinics" in the book. Each clinic consists of four case descriptions. After the descriptions there are discussions of each case including differential diagnosis and treatment. Then follow several multiple choice questions based on the cases in the section. The cases are grouped in no particular order, and one can go through the four cases in each clinic much more quickly than is usually necessary for a published clinicopathologic conference. A brief index at the end makes it possible to find the case representing a particular diagnostic problem.

I enjoyed going through this book because in this era of self-assessment examinations, there was instantaneous feedback (and perhaps also because I picked most of the diagnoses correctly). The cost, however, seems to be on the high side for a paperback.

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PHYSICIAN'S HANDBOOK—Eighteenth Edition—Marcus A. Krupp, MD, Clinical Professor of Medicine, Stanford University School of Medicine, Director of Research, Palo Alto Medical Research Foundation, Director of Laboratories, Palo Alto Medical Clinic; Norman J. Sweet, MD, Associate Professor of Medicine, San Francisco General Hospital, University of California, San Francisco; Ernest Jawetz, PhD, MD, Professor and Chairman, Department of Microbiology, Professor of Medicine, Lecturer in Pediatrics, University of California, San Francisco; Edward G. Biglieri, MD, Professor of Medicine, Chief of Endocrine Services, San Francisco General Hospital, University of California, San Francisco; and Robert L. Roe, MD, Assistant Clinical Professor of Medicine, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1976. 754 pages, $8.00.

Physician's Handbook is a small but plump book measuring 10.5 cm by 17.7 cm by 2.5 cm thick. For those needing conversion factors, they may be found in Table 3, page 714 of the volume. As were previous editions of the book, this edition is well bound with a flexible cover reasonably resistant to moisture and other contaminants that might be found in the working milieu of a physician.

This volume has as its primary audience medical students and house officers; it contains an extraordinarily complete set of data analysis—all that an average physician might need. No space is wasted including the inside of the covers of the book.

The book deals with the interpretation of the data base that one might gather in examining and testing a patient. This material is supplemented with sections detailing certain diagnostic and therapeutic procedures and the utilization of some therapeutic modalities, such as particular drugs, hormones, oxygen and aerosol therapy. There is a very interesting chapter on the utilization of diets.

The first three chapters—which have to do with emergency medical examination, outlines for history taking and physical examination, and neurologic diagnosis—represent a useful review for any physician in any specialty. I particularly liked the chapter on endocrine function and tests and felt that it was up-to-date and useful for practicing physicians. This volume is not meant to be used as a test for the management of disease states but rather as a quick reference volume which will give you a way to interpret the findings of almost any procedure that you might ask for in the examination and testing of a patient.

The volume deserves a place among the reference books of any physician involved in the primary care of patients. It will probably be this type of volume against which the value of computers, as an information service, will be measured. If, as has been prophesied, doctors will some day have a computer terminal on their desk, that terminal will have to have information as quickly and readily accessible as one can find in a volume of this sort. I think the computer will find this a difficult task.

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RECENT ADVANCES IN UROLOGY—Number Two—Edited by W. F. Hendry, ChM, FRCS, Consultant Urologist, St. Bartholomew's Hospital, Royal Marsden Hospital and Chelsea Hospital for Women; Senior Lecturer, Institute of Urology, London. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 353 pages, $32.50.

The title is somewhat misleading. The preface quite accurately states that "Many of the chapters have deliberately included much basic information . . . " and this factor quickly becomes evident to the reader. It therefore seems to this reviewer that a fitting title would be "Current Concepts in Urology."

The volume is a very "meaty" compendium of current thought and knowledge in the various aspects of the urologic specialty. There are 15 contributors in addition to the editor, W. F. Hendry. The latter contributes in whole or in part to four of the chapters. The contributors all appear to be well chosen for knowledge and competence in their respective sections.

There are areas of criticism of course. In the chapter devoted to the biochemical aspects of stone disease, I felt that there was room for further discussion of therapy with phosphates. Furthermore I did not find reference to the work of Prien and others with magnesium. The author of this section accepts the diagnosis of "idiopathic hypercalciuria" as though this common enough term was a truly definitive term rather than a working hypothesis. The chapter on urinary tract infections is quite up-to-date but I thought that there was room for more in depth discussion of chemotherapy.

I particularly enjoyed the chapters on obstructive uropathy in children and those on renal replacement therapy and urothelial neoplasia. They are concise and very readable statements on these complicated subjects.

This volume is particularly well suited to internists and general practitioners. American readers will find a few confusing variations in terminology, such as in catheter and medication names, but the issue is a minor one. I have often thought, however, that in those books containing technical terms and which are distributed in several English speaking countries where there is a variation in usage, a brief section giving the terminology counterparts would be worthwhile.

THOMAS F. CONROY, MD
San Mateo, CA

TRACTION AND ORTHOPAEDIC APPLIANCES—John D. M. Stewart, MA (Cantab), FRCS (England), Consultant Orthopaedic Surgeon, Chichester & Graylingwell, and Worthing, Southlands & District Groups of Hospitals. Longman Inc., 19 West 44th St., New York City (10036), 1975. 206 pages, $19.00.

This book is written by an English orthopedic surgeon primarily for the use of orthopedic residents, nursing, and physiotherapy staff of hospitals with orthopedic wards. It contains detailed instruction on the application of a variety of kinds of traction, both common and uncommon. These details are not normally found in standard texts. For those with an interest in historical aspects of traction the references are excellent. The sections on traction are clearly the best part of the book.

The usefulness of the book is limited for the American audience by the recommendation of British products. Some terminology is unfamiliar to the American reader. The term zinc oxide strapping rather than adhesive tape is an example. Two sections of this text seem curiously out of place. Several pages are devoted to clinical tests for instability of the newborn hip and the final chapter is devoted to tourniquets. While both are well written, they seem inappropriate.

The weakest portion of the book is the section on bracing and footwear. The different materials available to orthotists and the differing uses of plastics are such that this section is not useful for an American audience.

While there are interesting and informing sections in this book, its spottiness makes it difficult to recommend. I would agree with the authors that its primary usefulness will be to those in training, but the price of $19.00 suggests that its use will be confined to hospital libraries.

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SURGICAL DISORDERS OF THE PERIPHERAL NERVES—Second Edition—Sir Herbert Seddon, CMG, Honorary Consulting Surgeon, Royal National Orthopaedic Hospital, London; Honorary Fellow, Worchester College, Oxford, Sometime Nuffield Professor of Orthopaedic Surgery, Oxford, and Professor of Orthopaedic Surgery, London. Church Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975. 336 pages, $39.00.

The second edition of Sir Herbert's splendid monograph, three years after the first edition, provides an opportunity to indicate the great value of this beautifully produced, well illustrated, authoritative and practical work on peripheral nerve injuries. Although the changes in the second edition are not major (the book is approximately the same length and has essentially the same organization and illustrations), some attention has been given to correcting errors in the first edition and giving additional emphasis to nerve grafting and so forth. One of the greatest values of this monograph is that it is written by the outstanding authority in the English language on the surgical management of peripheral nerve injuries. It is based upon Seddon's personal experience which is carefully weighed, criticized, and evaluated against the experience of others as sampled in the literature and from his colleagues in the field.

The monograph is logically constructed. The illustrations are pertinent to the text, are of sufficient size and are reproduced on such high quality paper that they are excellent tools to the student of the problem. The emphasis is clinical but the foundations of management are appropriately laid. When only empiricism pertains, Sir Herbert, with characteristic scientific honesty, so indicates. The reference list is comprehensive. One can identify only a rare error in the index. If one were to add any other criticism, it would be that one does not find comment about the recent developments in the use of electrical recording of nerve action potentials intraoperatively such as furthered by the work of Kline and co-workers. This volume should be looked upon as the standard clinical work in the field. It provides an excellent yardstick against which to compare other treatises, and as a single-authored book it has the richness of an individual writer's style, continuity and cohesiveness. It is highly recommended to all practicing in the field of neurological diagnosis and treatment, orthopedic surgeons and surgeons who manage trauma. It is a must for any general medical library and it should be the peripheral nerve injury reference book for medical students and nonsurgical physicians.

W. EUGENE STERN, MD
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Center for the Health Sciences

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TO BE AN INVALID—The Illness of Charles Darwin—Ralph Colp, Jr., MD, Acting Director of the Psychiatric Section, Columbia University Health Service. The University of Chicago Press, 5801 Ellis Avenue, Chicago (60637), 1977. 286 pages, $15.00.

Pathography, the clinical aspects of biography, has long fascinated both historians and physicians. The role of illness or disability in creative life, as for instance Beethoven's deafness, Dostoevsky's epilepsy or William Halsted's cocaine and subsequent morphine addiction, have long beguiled the biographer. Using Freud's techniques, psychological portraits such as Erik Erikson's *Young Man Luther*, or Freud himself on Leonardo and on Moses, have received much publicity in recent years. Hitler, Richard Nixon, Woodrow Wilson and Thomas Jefferson, are only a few of the many subjects for such studies.

The middle and latter 19th century seems to have been a particularly rife period for vague, disabling illnesses in numbers of otherwise prominent and successful people. Florence Nightingale, Charles Darwin, Henry as well as William James, Henry Adams, Elizabeth Browning, and many more, all suffered periods of great incapacity. Sir George Pickering has recently collected some of these pathographies in a book entitled *Creative Malady*. Nightingale and Darwin receive the most extended treatment by Sir George, who believes they used their psychologically induced symptoms to retreat from their social duties in order to get a great deal of their work done.

Charles Darwin's illness, especially manifested by nausea, vomiting and great weakness, has been the subject of numerous papers and several previous books. To Dr. Ralph Colp goes the credit for the most extensive study yet done, though his conclusions are really not terribly startling. Dr. Colp, who is Director of the Psychiatry Section, Columbia University Health Service, concludes his extensive research with the observation that psychological stresses were the most probable cause for Darwin's symptoms. On the way to this conclusion, Colp convincingly disposes of a number of previous theories such as Chagas disease contracted on the voyage of the Beagle, chronic arsenic poisoning from use of Fowler's solution and illness due to some form of inherited weakness. That Darwin lived more than 72 years, most of the last 50 of them plagued by illness, is some evidence that he was not suffering from a progressive organic disorder.

The intense psychological strain of creativity and the emotional burden of overthrowing church dogma and fighting the beliefs of many recognized scientists of his day apparently took an immense toll. Thus Colp maintains the theory of evolution was conceived and promulgated despite severe illness, not because of it as Pickering

argued. All in all, this is a very convincing book, easy to follow in its lines of argument, though occasionally Dr. Colp retreats to conjecture such as "may have been." For physicians interested in a good historical case study of one man's illness, plus a great deal of feeling for 19th century life and medicine, this is the book.

GERT H. BRIEGER, MD
Department of the History of Health Sciences
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THE JOINTS OF THE ANKLE—Verne T. Inman, MD, PhD, Professor Emeritus of Orthopaedic Surgery, University of California, San Francisco. The Williams & Wilkins Co., 428 E. Preston St., Baltimore (21202), 1976. 117 pages, $12.95.

This is a superb and classic monograph. It is clearly and carefully written. The author has been a premier investigator of gait for many years. He is a clinician with great proficiency in anatomy and biomechanics. The data presented have been gathered over a long period and are presented in a scholarly and well organized fashion. The book primarily deals with the ankle and subtalar joints. It dispels misconceptions about anatomy and physiology, elucidates generalizations regarding motion of the ankle and subtalar joints, and stresses individual variations. While this monograph will be of interest primarily to orthopedists, anatomists and those interested in biomechanics, it may also serve as a model of investigative techniques of joint motion.

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THE NORMAL LUNG—The Basis for Diagnosis and Treatment of Pulmonary Disease—John F. Murray, MD, Professor of Medicine and Member of the Senior Staff of the Cardiovascular Research Institute, University of California, San Francisco; Chief of Chest Division of the Medical Service, San Francisco General Hospital. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1976. 334 pages, $14.50.

Like many areas of medicine, respiration has had its own recent knowledge explosion due to major advances in anatomy, physiology, neurophysiology, biochemistry and immunology. This 334-page overview, written by an eminent chest physician, stems from the valid premise that the practice of respiratory medicine is based upon a sound understanding of normal lung function and structure and their interrelationship. Dr. Murray attempts to concisely present "as much of the new information about the lung" as possible in an informative, readable and effective format. The author has admirably succeeded in most of his 12 chapters. *The Normal Lung* is also a solid review of "classic" respiration. It, therefore, has considerable value for medical students, house staff, postdoctoral fellows and physicians in practice, as well as for basic scientists. However, preparation in some basic principles may be helpful, for example, in the chapter on ventilation. Physiologic interpretation of selected pulmonary function data is emphasized and not their method of measurement. For the latter, the reader is wisely referred to other sources.

The following topics are well explained and concisely explored: lung embryology and postnatal development, ventilation and perfusion, gas exchange, acid-base, neural regulatory mechanisms, exercise adaptations, defenses and age-related changes. The content is complete, current, accurate and generally excellent. Few overviews give much mention (let alone chapters) to new but essential areas such as pulmonary lymphatic and nervous systems, immunology and aging effects. The author repeatedly correlates structure and function and effectively uses clinical examples when they enhance the understanding of normal respiration. The individual chapter outlines are helpful to the reader as he progresses to new topics. The figures and tables are generally simple, strategically located, helpful and numerous (present in 60 percent of the book). Many previously unpublished illustrations are also present. References are quoted effectively, numerous (average of 48 per chapter) and current.

Although the immense amount of summarized data is written with authority and references, the author is the first to admit to the possible absence or controversy of certain topics, limitations of current knowledge and dangers of extrapolating animal data to the human biosystem. One is frequently stimulated by excellent, thought-provoking questions raised by the author. The few deficits in the book are mainly omissions of such matters as discussion of the occlusion pressure and breath-holding time in the chapter on regulation of ventilation. The chapter on defense mechanisms does not go "one step further" to briefly discuss the specific responses of the lung to immunologic injury. Gross anatomy is minimal. Only a single pulmonary angiographic illustration is used. Presentation of normal chest roentgenograms, bronchograms, bronchoscopic photographs and even chest computer tomographs might be effective teaching devices. Lung metabolism involving lipids, proteases and collagen is also lacking.

How does this book compare with the well-known texts on respiration? This book will not replace them, but will strongly complement and enhance any respiratory library because of its uniqueness in covering almost all aspects of normal respiration. It is complete and understandable. *The Normal Lung* is likely to become another classic.

HENRY GONG, JR., MD
Division of Pulmonary Disease
Department of Medicine
UCLA School of Medicine
Los Angeles, California 90024

* * *

FLUORESCENT PROTEIN TRACING—Fourth Edition—R. C. Nairn, MD, PhD(L'pool), FRCPath, FRCPA, FRACP, FRSE, Professor and Chairman, Department of Pathology and Immunology, Monash University; Honorary Consultant Pathologist, Alfred Hospital, Prince Henry's Hospital and Queen Victoria Memorial Hospital, Melbourne, Australia; Foreword by J. R. Marrack, DSO, MC, MA, MD(Cantab), Emeritus Professor of Chemical Pathology, University of London. Longman, Inc., Churchill Livingston - Medical Division, 19 West 44th St., New York City (10036), 1976. 648 pages, $45.00.

Fluorescent methods have become standard procedures in many laboratories for the detection of protein and antibody. Although the techniques have remained relatively unchanged over recent years, the applications have expanded considerably. There are few complete reviews and texts available specifically on this subject. One of the classics is provided by R. C. Nairn. The book is well organized and extensively covers details of fluorescent procedures. Methods are discussed in detail, with attention to conjugation of proteins, properties of conjugated proteins, the theory and use of fluorescent microscopy and the use of fluorescent methods for protein and antibody studies. The color photographs provided are extremely useful for those unfamiliar with various forms of fluorescence. The appendix is useful for carrying out specific procedures which are discussed in the main text. Extensive referencing has been given. Again, this is well organized, although I would question the value of providing more than 250 pages of references. The book should be extremely useful to those laboratories engaged in fluorescent methods.

ARTHUR J. AMMANN, MD
Director, Pediatric Immunology
Director, Pediatric Clinical Research Center
Associate Professor, Pediatrics
University of California, San Francisco

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Washington State Medical Association

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Former Assistant Secretary for Health, U.S. Department of Health, Education, and Welfare
- **The Good and the Bad About the Government's Impact on Medical Care**

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- **The Federated Council for Internal Medicine—What It Does for the Internist**

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- **Medical Treatment of Stable Coronary Heart Disease**

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Professor and Chairman, Department of Anesthesiology, University of Utah
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(Continued on Page 20)

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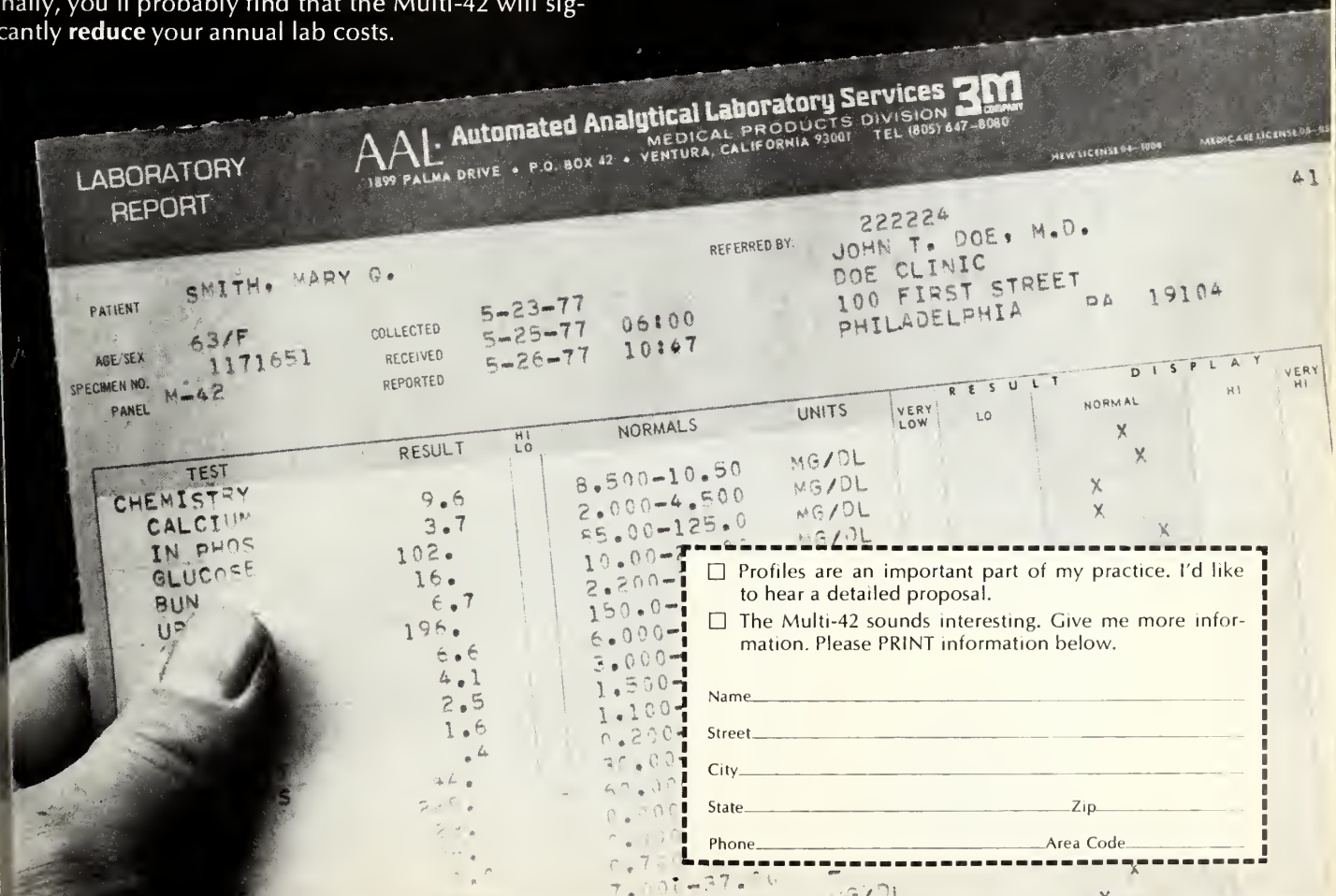

(Continued from Page 18)

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33 YEAR OLD BOARD CERTIFIED PULMONARY PHYSICIAN with expertise in fiberoptic bronchoscopy desires partnership or hospital associated practice in Southern California. Available summer 1978. Contact John Donaldson, 13107 Beaver Terrace, Rockville, MD 20853.

33 YEAR OLD OB AND GYN Board eligible, chief resident University Hospital, New York, trained in laproscopy and fetal monitoring. Board Certified Surgery, England. Dr. N. Gupta, 8B, 1650 Selwyn Avenue, Bronx, NY 10457; (212) 731-7161.

OPHTHALMOLOGIST—Board Certified, 34 years old. Desires to buy existing practice or set up solo where needed. All areas considered. Box 5933, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

RHEUMATOLOGIST/INTERNIST, 32, University trained, ABIM certified, board eligible Rheumatology, seeks position beginning Summer 1978. Reply Box 5932, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ANESTHETIST—available San Francisco Area. Free lance basis. Experienced all techniques. Anesthesia Services. (415) 391-3339.

PRACTICE FOR SALE

INTERNIST board qualified or certified in internal medicine. Preferably sub-specialty in pulmonary disease to assume solo practice of chest physician retiring October 1, 1977 fully staffed hospital. Will introduce to community. Hospital contract also a possibility. Ventura County area. Reply Box 5943, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

MEDICAL EQUIPMENT FOR SALE

ENOUGH USED EQUIPMENT to furnish a busy solo or 2-man general practice. Will furnish two exam rooms (includes deluxe tables), an ENT room, treatment room, lab, and receptionist area. For sale as a package only. No dealers. $3,000. Write to Box 5941, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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DOCTORS' OFFICES—4,000 sq. ft. air conditioned solid concrete building. Excellent condition. Now rented. 29 percent down. Call agent (209) 847-1442.

HAWAII RENTAL

HAWAIIAN (Hanalei, Kauai) VACATION beach home for only $250 per week. Old Hawaiian atmosphere, away from crowded beaches. Not a cramped condo, but a full house with large yard and open space. Excellent skin diving, swimming and beaches. Sleeps 12. Monthly rate $950. For details, pictures and information, write:

JAMES R. CHRISTIANSEN
1216 State Street
Santa Barbara, CA 93101
Tel. (805) 962-8141

OFFICES TO LEASE OR RENT

MEDICAL DENTAL UNIT for rent. Available in 2 months. Will remodel to suit. B Berger, MD, 1063 San Pablo, Pinole, CA 94564, (415) 758-2511.

REDWOOD CITY—Leasing custom designed professional office equipped with 2 examination rooms—suitable for one or two doctors. Close to buses, downtown and hospitals. Adequate parking. Common area maintenance. Call building manager: (415) 365-4593.

PARK CITY MEDICAL CLINIC for lease. Fully equipped, 1,100 sq. ft. includes x-ray, lab, sleep room. Live in, walk to ski, tennis, golf, town. Inquire P.O. Box 547, Park City, Utah 84060.

FOR RENT: Pleasant Doctor's Office, fully equipped, including x-ray and approximately 1,500 active patient charts. Room for one or two doctors. Quiet town of 2,500 in beautiful farming area of the San Joaquin Valley. Ready to walk in and practice. Ten and fifteen minutes from four hospitals. One other MD in town. Gilbert den Dulk, P.O. Box 636, Ripon, CA 95366.

HAWAII RENTAL

WAIKIKI: Luxury condominums near beach, 1-bedroom. High ocean/town or Diamond Head view. $225. per week, $800 per month for 2. Write Kay-Jay, P.O. Box 88295, Honolulu, Hawaii 96815.

(Continued on Page 28)

CONTINUING MEDICAL EDUCATION

California, Hawaii • Oregon • Washington, Montana, Alaska, Idaho

CALIFORNIA and HAWAII

THIS LISTING of continuing education programs in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 146. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

CANCER

September 10—**An Update of Gynecologic Oncology.** See Obstetrics and Gynecology, September 10.

September 17—**Clinical Implications of New Diagnostic Techniques—Ultrasound, Cat Scan, Radioisotopes, Clinical Chemistry.** San Francisco Regional Cancer Foundation at Fireman Fund Building, San Francisco. Saturday. 4 hrs. Contact: Norma Schlager, PhD, S.F. Regional Cancer Foundation, 14th and Lake, San Francisco 94118. (415) 221-2132.

October 3-7—**Medical Oncology Review.** American College of Physicians and Huntington Memorial Hospital at Huntington Sheraton Hotel, Pasadena. Monday-Friday. 36 hrs. $140, ACP members; $200, nonmembers. Contact: Arlene Ellis, Coord., Med. Staff Affairs, Huntington Mem. Hosp., 100 Congress St., Pasadena 91105. (213) 440-5176.

November 18-19—**Endocrine Aspects of Cancer: New Perspectives.** Mt. Zion Hospital and Medical Center, San Francisco. Friday-Saturday. Contact: Ann Raisbeck, Dept. of Med. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2401.

January 30-31—**Cancer.** USC. Monday-Tuesday.

MEDICINE

September 7-11—**Medical Knowledge Self-Assessment Program Course.** American College of Physicians at Golden Gateway Holiday Inn, San Francisco. Wednesday-Sunday. 30 hrs. $140, ACP members; $200, nonmembers. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

September 14-16—**Pediatric Dermatology.** STAN. Wednesday-Friday. 23 hrs. $225.

September 20-November 8—**Current Practical Cardiology—1977.** Daniel Freeman Memorial Hospital, Inglewood. Tuesdays, 6:30-9:00 p.m. 16 hrs. $100 (includes dinner with each session). Contact: Donald A. Dennis, PhD, Dir. of Med. Ed., Daniel Freeman Memorial Hosp., 333 N. Prairie Ave., Inglewood 90301. (213) 674-7050, ext. 127.

September 26-30—**Medical Knowledge Self-Assessment Program Course.** American College of Physicians at Hilton Hotel, Los Angeles. Monday-Friday. 30 hrs. $140, ACP members; $200, nonmembers. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

September 29-30—**Annual Physician Postgraduate Symposium on Heart Disease.** San Francisco Heart Assn. and Council on Atherosclerosis, American Heart Assn., at Golden Gateway Holiday Inn, San Francisco. Thursday-Friday. Contact: Molly Austin, Assoc. Dir., S.F. Heart Assn., 421 Powell, San Francisco 94102. (415) 433-2273.

September 29-30 — **Clinical Immunology/Arthritis Update.** UCSF. Thursday-Friday. 13 hrs. $125.

October 1-8—**Cardiology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

October 3-7—**Medical Oncology Review.** See Cancer, October 3-7.

October 5—**Digitalis: New Insights at the Bicentennial.** L. A. Society of Internal Medicine at L.A. Co. Med. Assn., Los Angeles. Wednesday. 1½ hrs. $7.50 for dinner. Contact: Thomas T. Yoshikawa, MD, LASIM, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

October 5-6—**American Heart Association, Greater Los Angeles Affiliate—45th Annual Fall Symposium and 10th Annual Griffith Lecture.** Hilton Hotel, Los Angeles. Wednesday-Thursday. 12 hrs. $65, member of any Heart Assn.; $85, nonmember. Contact: LaVerna Titus, AHA, Greater L.A. Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

October 5-December 7—**Gastroenterology for the Practicing Internist.** UCLA. Wednesday evenings. $200.

October 6-7—**Pediatric Nephrology.** UCSF. Thursday-Friday.

October 7-8—**Practical Dermatopathology.** STAN at Holiday Inn, Palo Alto. Friday-Saturday. 16 hrs. $150; $100, residents

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

and those in training. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Med. Ctr., Stanford 94305. (415) 497-6101.

October 8-15—**Endocrinology/Nephrology Review.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

October 10-14—**Practical Electro-Cardiography.** Memorial Hospital Medical Center of Long Beach-UCI at Hotel Inter-Continental, Maui, Hawaii. Monday-Friday. $150. Contact: Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

Ocober 11-14—**Electrocardiography: Core Curriculum and Self-Assessment.** PMC at Golden Gateway Holiday Inn, San Francisco. Tuesday-Friday.

October 21-22—**Internal Medicine Symposium—22nd Annual.** Southern Calif. Permanente Medical Group at Hilton Hotel, Pasadena. Friday-Saturday. Contact: Shirley Gach, So. Calif. Permanente Med. Grp., 4900 Sunset Blvd., Rm. 6014, Los Angeles 90027. (213) 667-4241.

October 21-23—**Practical Cardiology—1977.** American College of Cardiology at Del Monte Hyatt Hotel, Monterey. Friday-Sunday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Division of Continuing Education, ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

October 26—**Consultations in Hypertensions.** UCSD at Vacation Village, San Diego. Wednesday.

October 28-29—**Diabetes.** STAN and Santa Clara County Diabetes Society at Palo Alto Medical Clinic. Friday-Saturday.

October 30-November 3—**American College of Chest Physicians—43rd Annual Scientific Assembly.** MGM Grand Hotel, Las Vegas. Sunday-Thursday. Contact: Dale E. Braddy, MS, Dir. of Education, ACCP, 911 Busse Highway, Park Ridge, IL 60068.

ovember 3-6—**California Society of Internal Medicine—Annual Meeting.** Canyon Hotel, Palm Springs. Thursday-Sunday. Contact: CSIM, 703 Market St., Suite 1412, San Francisco 94103. (415) 362-1548.

ovember 4-5—**Mechanisms of Hemostasis and Thrombosis: Experimental and Clinical Perspectives.** PMC at Fairmont Hotel, San Francisco. Friday-Saturday.

ovember 7-11—**Pediatric Allergy and Clinical Immunology.** UCSF. Monday-Friday.

ovember 7-16—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. 10 days. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Division of Continuing Education, ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

ovember 9—**Endocrinology Seminar.** LLU. Wednesday. 4 hrs. $25.

ovember 10-12—**Diagnosis and Management of Diseases of Peripheral Nerves and Muscle.** UCSD at Hilton Hotel, San Diego. Thursday-Saturday. 14 hrs. $125.

ovember 17-19—**Unusual Problems in Pulmonary Disease.** USC at Erawan Gardens, Palm Springs. Thursday-Saturday.

ovember 26-December 3—**Lymphoproliferative Disorders.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

ecember 2-4—**Advances in Heart Disease—1978.** American College of Cardiology at Fairmont Hotel, San Francisco. Friday-Sunday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Division of Continuing Education, ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

ecember 7—**Lyman A. Brewer III Cardiothoracic Symposium —3rd Annual.** LLU at Hilton Hotel, Los Angeles. Wednesday. 8 hrs. $50.

ecember 10—**Pulmonary Artery Catheters and Ventilators.** PMC. Saturday. 6 hrs. $300.

ecember 12—**Current Concepts in Ileitis and Colitis.** UCD at Red Lion Motor Inn, Sacramento. Monday.

anuary 11—**Management of Arrhythmias.** LLU. Wednesday. hrs. $25.

January 20-21—**Stress Testing: A New Look Forward to New Developments—Backward to Old Concepts.** American College of Cardiology at Memorial Hospital Medical Center, Long Beach. Friday-Saturday. Contact: Miss Mary Ann McInerny, Dir., Extramural Programs Dept., Div. of Cont. Ed., ACC, 911 Old Georgetown Rd., Bethesda, MD 20014.

January 21—**Systemic Disease/Eye, Mouth, Skin Manifestations.** See Of Interest to All, January 21.

January 25-27—**Advances in Neurology.** UCSF at Hyatt on Union Square, San Francisco. Wednesday-Friday.

January 28—**Management of Fluid, Electrolyte and Acid-Base Disorders.** STAN. Saturday. 7 hrs.

OBSTETRICS AND GYNECOLOGY

August 27-September 2—**Edward Tyler Symposium on the Practical Management of the Infertile Couple.** Tyler Medical Clinic, Los Angeles, and Univ. of Hawaii School of Medicine at Royal Lahaina Hotel, Maui, Hawaii. One week. 16 hrs. $125. Contact: Exclusive Travel, 3345 Wilshire Blvd., Los Angeles 90010.

September 10—**An Update of Gynecologic Oncology—17th Annual Fall Seminar in Obstetrics and Gynecology.** Shufelt Society of Santa Clara Valley at Hyatt House, San Jose. Saturday. 7 hrs. Contact: Robert Floyd, Jr., MD, 175 N. Jackson Ave., San Jose 95116.

September 30-October 1—**Office Gynecology Workshop.** PMC. Friday-Saturday.

A Symposium:

MECHANISMS OF HEMOSTASIS AND THROMBOSIS:

Experimental and Clinical Perspectives

NOVEMBER 4-5, 1977

FAIRMONT HOTEL • SAN FRANCISCO

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This advanced course is designed to elucidate the latest research efforts of selected investigators on the mechanisms of platelet participation in hemostasis and thrombosis. The program will bring into focus the state of the art in the diagnosis and treatment of hematologic disorders and is approved for continuing education credit.

Proceedings will be available in printed and taped form.

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Space is limited, so register early.

Pacific Medical Center

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SEPTEMBER 30-OCTOBER 1
Office Gynecology Workshop
OCTOBER 8
Office Emergencies for Medical and Dental Assistants
OCTOBER 22
Selected Topics in Infectious Disease
OCTOBER 27-28
Living with Chronic and Terminal Illness
OCTOBER 29
Audiology Update for Primary Physicians
NOVEMBER 4-5
Mechanisms of Hemostasis and Thrombosis
NOVEMBER 18
Preparing for Legal Testimony
NOVEMBER 18-19
Strabismus
DECEMBER 3-5
ENG Workshop
DECEMBER 10
Pulmonary Artery Catheters and Ventilators
DECEMBER 10
PERT Workshop

For information, write
Dept. of Continuing Education
Pacific Medical Center
P.O. Box 7999, San Francisco, CA 94120
Tel. (415) 563-4321

October 12-16—**Pacific Coast Fertility Society—Annual Meeting.** Canyon Hotel, Palm Springs. Wednesday-Sunday. 21 hrs. $15, member; $25, nonmember. Contact: Ronald S. Swerdloff, MD, PCFS, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

October 17-21—**Obstetrics/Gynecology Review.** USC at Beverly Hilton Hotel, Beverly Hills. Monday-Friday.

October 28—**Advances in Obstetrics and Gynecology—11th Annual Meeting.** Northern Calif. Obstetrical and Gynecological Society at Red Lion Motor Inn, Sacramento. Friday. 7 hrs. Contact: Benjamin J. Berry, MD, Prog. Chr., NCOGS, 3720 Mission Ave., Carmichael 95608. (916) 481-5401.

November 10-12—**Menopause, Fetal Monitoring, and Genetics.** UCSF at Mark Hopkins Hotel, San Francisco. Thursday-Saturday.

November 12-14—**Comprehensive Laparoscopy: Current Principles and Practice.** UCSD at Kona Kai Club, Kona, Hawaii. Saturday-Monday.

November 12-19—**Endocrinology—Infertility.** UCSF at Kaui Surf, Kaui, Hawaii. One week.

January 14-21—**Perinatal Medicine.** USC at Royal Lahaina, Maui, Hawaii. One week.

January 28-30—**Comprehensive Laparoscopy.** UCSD at Kona Kai Club, San Diego. Saturday-Monday. 16 hrs. $375.

PEDIATRICS

September 14-16—**Pediatric Dermatology.** See Medicine, September 14-16.

September 15-16—**Pediatric Urology.** See Surgery, September 15-16.

September 28-29—**Brennemann Memorial Lectures—34th Annual.** L.A. Pediatric Society at Bonaventure Hotel, Los Angeles. Wednesday-Thursday. Contact: Eve Black, Exec. Sec., LAPS, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

October 1—**Clinical Problems in Immunology—Annual Pediatric Seminar.** Permanente Medical Group, Oakland. Saturday. Contact: Stephen L. McMurtry, MD, Dept. of Ped., Kaiser Hospital, 975 Sereno Dr., Vallejo 94590.

October 6-7—**Pediatric Nephrology.** See Medicine, October 6-7.

October 15-22—**Pediatrics for the Practitioner.** Children's Hospital of Long Beach and American Academy of Pediatrics. Chapter 2, at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. Contact: Margaret Frederick, Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 21-22—**Adolescence Sexuality and Related Problems** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday

November 4-5—**Children's Experiences of Health and Illness** UCD at Claremont Hotel, Berkeley. Friday-Saturday.

November 7-11—**Pediatric Allergy and Clinical Immunology** See Medicine, November 7-11.

December 3—**Practical Aspects of Sports Medicine for Pediatricians.** American Academy of Pediatrics, Calif. Chapter I Dist. IX, at Union Square Holiday Inn, San Francisco. Saturday. Contact: Martin Gershman, MD, 595 Buckingham Way, San Francisco 94132.

January 26-28—**Troubled Youth.** See Psychiatry, January 26-28

January 27-29—**Pediatric Anesthesiology.** See Surgery and Anesthesiology, January 27-29.

PSYCHIATRY

August 28-September 3—**VI World Congress of Psychiatry** World Psychiatric Association and American Psychiatri Association at Sheraton-Waikiki Hotel, Honolulu. Sunday Saturday. Contact: Rosa Torres, APA, 1700 18th St., N.W Washington, DC 20009.

September 23-24—**The Hysterical Personality.** UCD at Claremont Hotel, Berkeley. Friday-Saturday. 8 hrs. $85.

September 24-25—**Mind Altering Drugs in Clinical Practice** UCLA. Saturday-Sunday. 14 hrs. $140.

October 1-2—**Stress Management and Approaches to Stress** See Of Interest To All, October 1-2.

November 14-18—**Group Therapy Seminars.** UCSF at Merri Hotel, Oakland. Monday-Friday.

January 10-March 21—**Intensive Review of Psychiatry.** USC Tuesday evenings.

January 20-22—**A Retrospective Psychoanalytically Oriente Psychotherapy.** UCSF. Friday-Sunday.

January 26-28—**Troubled Youth.** USC at Vacation Village, Sa Diego. Thursday-Saturday.

RADIOLOGY AND PATHOLOGY

September 14—**Diagnostic Radiology.** LLU. 4 hrs. $25.

September 17—**Radiology Symposium—5th Annual.** Souther Calif. Permanente Medical Group at Bonaventure Hote Los Angeles. Saturday. Contact: Shirley Gach, So. Cali Permanente Med. Grp., Education and Research Dept., 490 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

September 17—**Clinical Implications of New Diagnostic Techniques—Ultrasound, Cat Scan, Radioisotopes, Clinical Chemistry.** See Cancer, September 17.

October 8-16—**Body Imaging Conference—2nd Annual.** We Park Hospital, Canoga Park, at Kauai Surf Hotel, Kaua Hawaii. One week. 25 hrs. $295. Contact: Ronald J. Frei man, MD, Dept. of Radiology, West Park Hospital, 224 Roscoe Blvd., Canoga Park 91304.

October 21-23—**Society of Nuclear Medicine—2nd Annu Western Regional Meeting.** Aladdin Hotel, Las Vegas. Fr day-Sunday. Contact: Justine J. Lynch, P.O. Box 40279, Sa Francisco 94140. (415) 647-0722 or (415) 647-5909.

January 16-20—**Computed Tomography.** UCSF at Fairmo Hotel, San Francisco. Monday-Friday. $295.

'ostgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 15 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

URGERY AND ANESTHESIOLOGY

ıugust 15-20—**Intensive Review of Orthopaedic Surgery.** J. Vernon Luck Research Society at Airport Park Hotel, Inglewood. Monday-Saturday. $400. Contact: Chadwick F. Smith, MD, 2400 S. Flower St., Los Angeles 90007.

ıugust 20-21—**Recent Advances in Respiratory Therapy.** California Society of Anesthesiologists at Sahara Hotel, Lake Tahoe. Saturday-Sunday. Contact: CSA, 100 S. Ellsworth Ave., No. 806, San Mateo 94401. (415) 348-1407.

ugust 22-24—**The Knee in Sports.** American Academy of Orthopaedic Surgeons at Hilton Hotel, San Francisco. Monday-Wednesday. $150, members; $200, nonmembers. Contact: AAOS, 430 N. Michigan Ave., Chicago 60611. (312) 822-0970.

ugust 27-September 2—**Edward Tyler Symposium on the Practical Management of the Infertile Couple.** See Obstetrics and Gynecology, August 27-September 2.

ptember 9—**Complications in Orthopaedic Surgery—11th Annual Orthopaedic Symposium.** Southern California Permanente Medical Group at Sheraton Motor Inn, Anaheim. Friday. Contact: Shirley Gach, So. Calif. Permanente Med. Grp., 4900 Sunset Blvd., Room 6014, Los Angeles 90027. (213) 667-4241.

ptember 9-10—**Vascular Surgery.** UCSF. Friday-Saturday.

ptember 10-17—**Anesthesia.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

ptemper 14-15—**Vestibular Functions.** USC. Wednesday-Thursday.

ptember 15-16—**Pediatric Urology.** UCD at Hyatt Lake Tahoe. Thursday-Friday. 10 hrs. $150.

ptember 16-17—**Ophthalmology Update III.** PMC at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. 13 hrs. $225.

ober 10-14—**Congress of Neurological Surgeons.** Hilton Hotel, San Francisco. Monday-Friday. 40 hrs. $75, members; $100, nonmembers. Contact: David L. Kelly, Jr., MD, Bowman Gray School of Medicine, Winston-Salem, NC 27103. (919) 727-4653.

ober 12-16—**Pacific Coast Fertility Society—Annual Meeting.** See Obstetrics and Gynecology, October 12-16.

ober 23-November 4—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200 for otolaryngologists; $900, residents. Contact: Malcolm D. Graham, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

ober 28-29—**The Macula.** Retina Research Fund of St. Mary's Hospital and Medical Center at Hyatt on Union Square, San Francisco. Friday-Saturday. Contact: Claire Chiyon, c/o Howard Schatz, MD, 3637 Sacramento St., San Francisco 94118. (415) 921-4860.

ober 30-November 4—**American Society of Plastic and Reconstructive Surgeons—Annual Convention.** Hilton Hotel, San Francisco. Sunday-Friday. 33 hrs. Contact: Linda Campbell, ASPRS, 29 E. Madison St., Chicago 60602. (312) 641-6593.

emper 3-5—**Nerve Repair: Clinical and Experimental Basis.** UCSF. Thursday-Saturday.

ember 5—**Review of Retinal Disease and Surgery.** The Retina Research Fund of St. Mary's Hospital at Hyatt on Union Square, San Francisco. Saturday. 7 hrs. Contact: Howard Schatz, MD, 3637 Sacramento St., San Francisco 94118.

University Extension
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A SPECIAL ONE DAY SEMINAR IN SACRAMENTO

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Sacramento attorneys LenArd S. Zipperian and Donald Lamp cover all aspects of estate planning, focusing on the implications of the Tax Reform Act of 1976 for physicians and surgeons.

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Fee: $50 (includes lunch).

For information contact
Box EL, University Extension, UCD
Davis, CA 95616
or call Eileen Leung at (916) 752-3347

November 12—**Current Concepts in Ophthalmic Plastic Surgery.** Jules Stein Eye Institute, Los Angeles. Saturday. Contact: Shelley E. Reid, Jules Stein Eye Institute, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

November 18-19—**Strabismus.** PMC. Friday-Saturday. 16 hrs.

November 19-20—**American Society of Anesthesiologists—Regional Refresher Course.** Sahara Hotel, Lake Tahoe. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

November 30-December 1—**Annual Ophthalmology Program.** UCSF. Wednesday-Thursday.

November 30-December 3—**Applied Biomechanics for Orthopedic Surgeons.** UCLA. Wednesday-Saturday. 23 hrs. $200.

December 2-4—**ENG Workshop.** PMC at Ilikai Hotel, Honolulu. Friday-Saturday. 24 hrs. $395.

December 3—**Emergency Anesthesia.** Sacramento Valley Anesthesia Society; UCD; Calif. Society of Anesthesiologists at Red Lion Motor Inn, Sacramento. Saturday. $50. Contact: John H. Eisele, MD, Dept. of Anesthesiology. UCD Sch. of Med., Davis 95616. (916) 752-2703.

December 14—**Treatment of Parkinsonism and Modern Concepts.** LLU. Wednesday. 4 hrs. $25.

January 5-7—**Anesthesia Update '78.** UCSD at Hotel Del Coronado, Coronado. Thursday-Saturday. 15 hrs. $150.

January 16-20—**Otologic Surgery—13th Annual Course.** Ear Research Institute, Los Angeles. Monday-Friday. 45 hrs. $500. Contact: F. H. Linthicum, Jr., MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

January 27-29—**Pediatric Anesthesiology—16th Clinical Conference.** Children's Hospital, Los Angeles. Friday-Sunday. Contact: Wayne Herbert, MD, 4650 Sunset Blvd., Los Angeles. (213) 663-3341, ext. 2262.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

August 15-19—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Islandia Hotel, San Diego. Sunday-Thursday.

August 22-27—**Family Practice Refresher Course—5th Annual.** UCD at Del Monte Hyatt House, Monterey. Monday-Saturday. 30 hrs. $225.

August 27-September 2—**Edward Tyler Symposium on the Practical Management of the Infertile Couple.** See Obstetrics and Gynecology, August 27-September 2.

August 29-September 3—**Family Practice Refresher Course—8th Annual.** UCI at South Coast Plaza Hotel, Costa Mesa. Monday-Saturday.

August 30-October 18—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland. Tuesday evenings.

September 6-October 25—**Family Practice.** USC. Tuesday evenings.

September 10-12—**The Physician in Mid-Career: Stress and Coping.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Saturday-Monday. 13 hrs. $135.

September 11-15—**Emergency Medical Care Symposium.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Thursday. 37 hrs. $175.

September 14-15—**Vestibular Functions.** See Surgery, September 14-15.

September 15-April 20—**Differential Diagnosis.** USC. Thursday evenings.

September 24-25—**Mind Altering Drugs in Clinical Practice.** See Psychiatry, September 24-25.

September 24-25—**National Symposium on Patient Education.** UCSF; American Hosp. Assn.; National Bureau for Health Education; National Center for Health Education, Inc.; Society for Public Health Education, No. Calif. Chapter; Stanford Univ. Hospital at UCSF. Saturday-Sunday. $65.

September 25-30—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Town and Country Hotel, San Diego. Sunday-Friday.

September 26-30—**Topics in Emergency Medicine—Postgraduate Course for Career Emergency Physicians.** UCSF at Ralph K. Davies Medical Center, San Francisco. Monday-Friday. 40 hrs. $300.

October 1-2—**Practical Nephrology for the Primary Care Physician.** UCLA. Saturday-Sunday.

October 1-2—**Stress Management and Approaches to Stress.** UCSF at Sheraton Palace Hotel, San Francisco. Saturday-Sunday.

October 3-7—**Primary Care.** STAN. Monday-Friday.

October 5-9—**Pharmacology—Rational Basis of Therapeutics.** UCSF at Hilo, Hawaii. Wednesday-Saturday. $225.

October 6-8—**Western Occupational Health Conference—21st Annual.** Western Occupational Medical Assn. at Fairmont Hotel, San Francisco. Thursday-Saturday. Contact: B. H. Bravinder, Exec. Sec., WOMA, P.O. Box 201, Alamo 94507. (415) 837-0874.

October 8—**Hormones and Sexuality, Part I.** UCLA. Saturday. $65 for both parts; $35, one part.

October 10-13—**American Academy of Family Physicians.** Hilton Hotel, Las Vegas. Monday-Thursday. Contact: AAFP, 1740 W. 92nd St., Kansas City, MO 64114.

October 12—**Pain and Its Management.** LLU. Wednesday. 4 hrs. $25.

October 12-16—**Pacific Coast Fertility Society.** See Obstetrics and Gynecology, October 12-16.

October 14-15—**Neurology for the Non-Neurologist.** Mt. Zion Hospital and Medical Center, San Francisco. Friday-Saturday. Contact: Ann Raisbeck, Dept. of Med. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2401.

October 14-16, 21-23—**Introduction to Sex Counseling Principles.** UCSF Human Sexuality Program at UCSF. Two weekends. 50 hrs. $175, per person; $300, per couple. Contact: Susan Hansen, Human Sexuality Program, 350 Parnassus, Suite 700, San Francisco 94143. (415) 666-4787.

October 17-21—**Family Practice Review—2nd Annual.** LLU. Monday-Friday. 30 hrs. $150.

October 22—**Selected Topics on Infectious Disease.** PMC. Saturday. 6 hrs. $80.

October 24-28—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday.

October 27-28—**Living with Chronic and Terminal Illness.** PMC. Thursday-Friday. 6 hrs. $60.

October 29—**Audiology Update for Primary Care Physicians.** PMC. Saturday. 6 hrs. $80.

October 29—**Hormones and Sexuality, Part II.** UCLA. Saturday. $65 for both parts; $35, one part.

October 30-November 3—**American Medical Association—Regional Meeting.** Sheraton Waikiki, Honolulu, Hawaii. Sunday-Thursday. Contact: AMA, 535 N. Dearborn, Chicago 60610.

October 31-November 4—**Intensive Care.** STAN. Monday-Friday.

November 5-6—**Practical Rheumatology for the Primary Care Physician.** UCLA and Arthritis Foundation, Southern California Chapter, at UCLA. Saturday-Sunday. 12 hrs. $145.

November 6-8—**Dermatology for the Family Practitioner.** UCD at Del Monte Hyatt House, Monterey. Sunday-Tuesday. 14½ hrs. $100.

November 6-9—**California Academy of Family Physicians—Annual Scientific Assembly.** Masonic Auditorium, San Francisco. Sunday-Wednesday. Contact: CAFP, 9 First St., San Francisco 94105. (415) 982-6091.

December 1-3—**Human Sexuality.** UCD at Hyatt Lake Tahoe, Incline Village. Thursday-Saturday.

December 2-4—**Sexual Dysfunction.** USC at SPA, Palm Springs. Friday-Sunday.

December 12-16—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Islandia Hotel, San Diego. Monday-Friday.

December 14—**Treatment of Parkinsonism.** See Surgery, December 14.

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January 18-20—**Infectious Disease.** USC. Wednesday-Friday.

January 19-21—**Medical Aspects of Aging.** UCLA at Valley Hilton Hotel, Sherman Oaks. Thursday-Saturday.

January 21—**Systemic Disease/Eye, Mouth, Skin Manifestations.** Continuing Medical Education/San Luis Obispo Consortium at Hilton Inn, San Luis Obispo. Saturday. 5 hrs. $25 for non-consortium members. Contact: Billy Mounts, MD, Chr., CME/SLO Consortium, P.O. Box 319, San Luis Obispo 93406.

January 23-27—**Therapy: Principles and Use of Drugs.** STAN. Monday-Friday. 27 hrs. $265.

January 23-27—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Town and Country Convention Center, San Diego. Monday-Friday. 40 hrs. $325.

January 23-27—**Topics in Emergency Medicine.** UCSF at Ralph K. Davies Medical Center, San Francisco. Monday-Friday.

January 27-28—**Nutrition.** UCSF. Friday-Saturday.

January 28-29—**Pediatric Update for Family Practitioners.** UCLA. Saturday-Sunday. 10 hrs. $135.

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RECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Physician-in-Residence Preceptorship in Pulmonary Disease. USC, Pulmonary Disease Section, Dept. of Medicine and Postgraduate Medical Education. One month or more, by arrangement. Opportunity for practicing physician to achieve specified knowledge and skills in adult pulmonary medicine. Contact: Oscar J. Balchum, MD, PhD, USC.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Department of Internal Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen R. Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, 97201.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

October 20-21—**Seventeenth Annual Postgraduate Course in Medicine and Surgery.** Providence Hospital, Department of Family Practice, 700 NE 47th, Portland 97213. Contact: Robert Cockburn, MD, 9204 SE Mitchell, Portland 97266.

INTERNAL MEDICINE

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

August 19-20—**Tomlin Memorial Cancer Lectures.** Rogue Valley Country Club, Medford. Contact: Earl L. Lawson, MD, The Medford Radiological Group, PO Box 1747, Medford 97501.

September 16-17—**Recent Developments in the Management of Infectious Disease.** Rogue Valley Country Club, Medford. Contact: J. S. Reinschmidt, MD, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

October 9-12—**Workshop in Electrocardiography.** Hilton Hotel, Portland. Contact: Henry J. L. Marriott, MD, Box 14405, St. Petersburg, FL 33733.

November 2-4—**Oregon Medical Association Annual Scientific Session.** Red Lion Motor Inn and Oregon Medical Association Headquarters, Portland. Contact: Sondra Gleason, Oregon Medical Association, 5210 SW Corbett Street, Portland 97201.

November 4-5—**Fourth Annual Critical Care Symposium.** Sheraton Hotel, Portland. Contact: J. S. Reinschmidt, MD, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

November 8—**Oregon Lung Association Sixth Annual Respiratory Disease Conference.** Sacred Heart Hospital, Eugene. Contact: Oregon Lung Association, 1020 SW Taylor, Portland 97205.

WASHINGTON, ALASKA, MONTANA AND IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-64, Seattle, Washington 98195. Phone: (206) 543-6995.

August 29-September 2—**American College of Physicians MKSAP Course.** Monday-Friday. Health Sciences Auditorium, Univ. of Wash., Seattle. 36 hrs. Members, $140; ACP Associates, $70; non-member physicians, $200; residents, research fellows, $140. Contact: American College of Physicians, 4200 Pine St., Philadelphia, PA 19104. (215) 243-1200 or Division of Cont. Med. Ed., SC-64, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495.

September 14-16—**Recent Advances in Gastrointestinal Surgery, Management of Trauma and Postoperative Care.** Wednesday-Friday, 8 a.m.-10 a.m. St Joseph's Hospital, Tacoma, Wash. 6 hrs. Fee to be determined. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

September 22-25—**Washington State Medical Association Annual Meeting.** Friday-Sunday. Washington Plaza Hotel, Seattle. Contact: Mr. Harlan Knudson, Exec. Dir., Washington State Medical Association, 900 United Airlines Bldg., Seattle, WA 98121. (206) 623-4801.

September 29-30—**Arthritis Foundation, Western Washington Chapter: Current Concepts in Arthritis.** Thursday-Friday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

September 29-October 1—**Montana Medical Association Annual Meeting.** Monday-Thursday. Village Motor Inn, Missoula, Mont. Contact: Mr. G. Brian Zins, Exec. Dir., Montana Medical Association, 2021 Eleventh Ave., Helena, MT 59601. (406) 443-4000.

October 4-7—**Antibiotics.** Tuesday-Friday. Tacoma General Hospital, Tacoma, Wash. 8 hrs. Fee to be determined. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

October 14-15—**Annual Cancer Conference.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

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***Usage in Pregnancy:* Several studies of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) suggest increased risk of congenital nalformations during the first trimester of pregnancy. Dalmane, a benzodiazepine, has not been studied adequately to determine whether it may be associated with such an increased risk. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. Consider possibility of pregnancy when nstituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Nc recommended for use in persons under 15 years of age. Thugh physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

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Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

References:

1. Kales A, *et al*: *Clin Pharmacol Ther 20*: 541-545, Nov 1976
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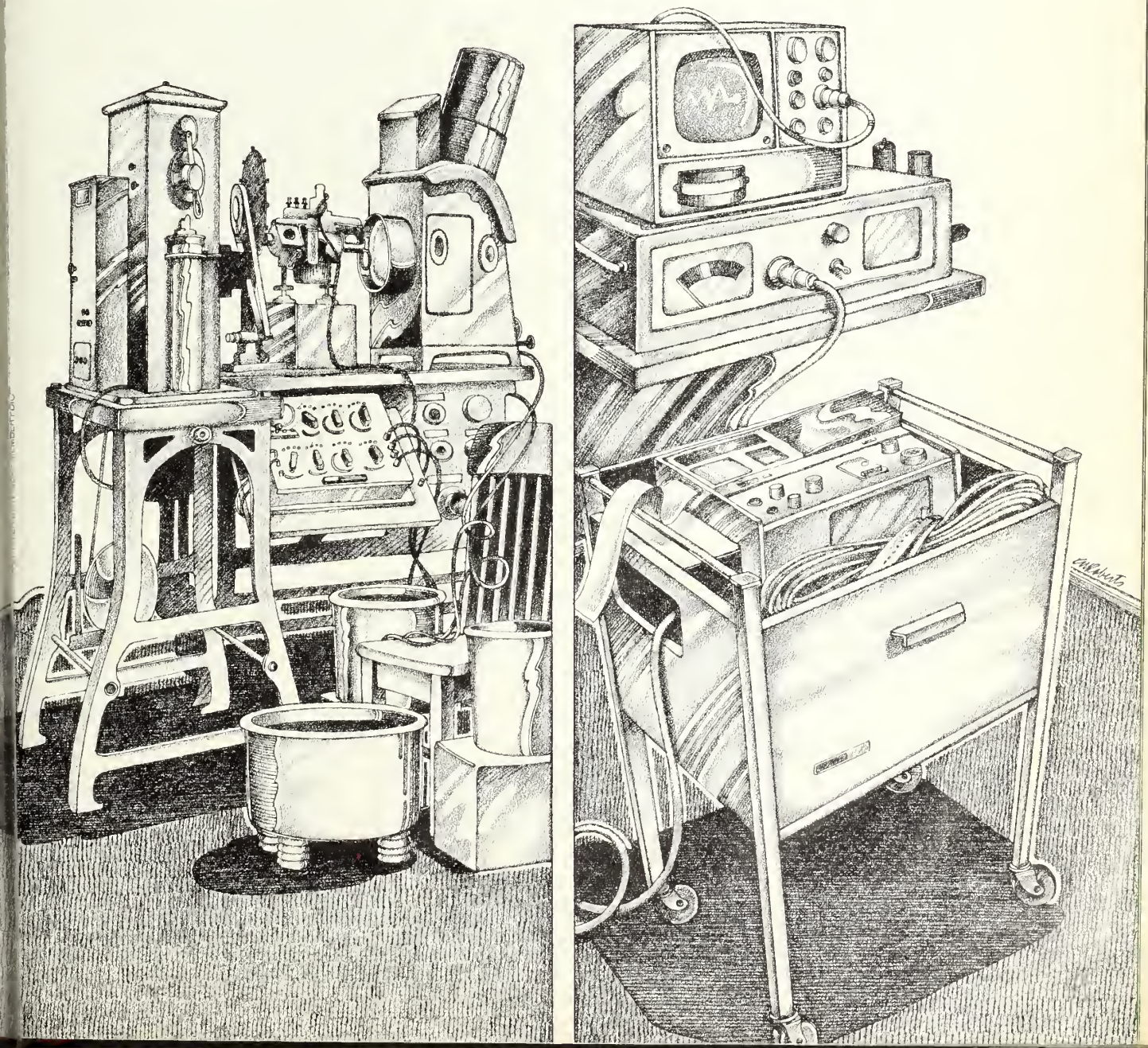

BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

THE EXPERIENCE OF DYING—E. Mansell Pattison, MD, Professor of Psychiatry and Human Behavior, Social Science, and Social Ecology, and Vice-Chairman, Department of Psychiatry and Human Behavior, University of California, Irvine. Prentice-Hall, Inc., Englewood Cliffs, NJ (07632), 1976. 335 pages, $10.95 (cloth), $4.95 (paperback).

FUTURE DIRECTIONS IN THE MANAGEMENT OF CARDIAC DISEASE—A Bicentennial Viewpoint: 7th Conference on Cardiovascular Disease in Snowmass-at-Aspen, 1976—Volume 20 in the Series: ADVANCES IN CARDIOLOGY—Editor: John H. K. Vogel, Santa Barbara, California. S. Karger, Basel, Switzerland. Albert J. Phiebig, Inc., US Representative of S. Karger, P.O. Box 352, White Plains, NY (10602), 1977. 144 pages, $31.50.

HANDBOOK: INTERACTIONS OF SELECTED DRUGS WITH NUTRITIONAL STATUS IN MAN—Donna Crawford March, RD. The American Dietetic Association, 430 North Michigan Avenue, Chicago (60611), 1976. 119 pages, $7.50.

HEALTHY PREGNANCY THE YOGA WAY—Judi Thompson. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1977. 147 pages, $3.95 (softbound).

HOW TO FEED YOUR HYPERACTIVE CHILD—Laura J. and George E. Stevens and Rosemary B. Stoner. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1977. 240 pages, $7.95.

INFECTIOUS DISEASES OF CHILDREN—Sixth Edition—Saul Krugman, MD, Professor of Pediatrics, New York University School of Medicine, formerly Chairman, Department of Pediatrics, Director of Pediatrics, Bellevue Hospital Center, and Director of Pediatrics, University Hospital, New York City; Robert Ward, MD, Emeritus Professor of Pediatrics, University of Southern California School of Medicine, formerly Physician-in-Chief, Children's Hospital, Los Angeles; and Samuel L. Katz, MD, Wilburt C. Davison Professor and Chairman, Department of Pediatrics, Duke University School of Medicine, Durham, North Carolina. The C. V. Mosby Company, 3301 Washington Blvd., St. Louis (63103), 1977. 539 pages, with 161 illustrations and 11 color plates, $29.50.

INTRODUCTION TO RESEARCH IN MEDICAL SCIENCES—A. Cuschieri, MD, ChM, FRCS(Ed), FRCS(Eng), Professor and Head of Department of Surgery, Uniiversity of Dundee; and P. R. Baker, BSc, PhD, Lecturer in Surgical Science, Department of Surgery, University of Dundee; Formerly, Lecturer, Department of Surgery, University of Liverpool. Longman Inc., 19 West 44th Street, New York, NY (10036), 1977. 216 pages, $10.50 (paperback).

LEUKEMIA AND LYMPHOMA IN THE NERVOUS SYSTEM—Edited by Carl Pochedly, MD, Director, Pediatric Hematology, Nassau County Medical Center, East Meadow, New York. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, IL (62717), 1977. 229 pages, $23.50.

LIVE LONGER NOW: The First One Hundred Years of Your Life: The 2100 Program—Jon N. Leonard, Jack L. Hofer and Nathan Pritikin. Grosset & Dunlap, Inc., 51 Madison Avenue, New York City (10010), 1974. 232 pages, $2.95 (paperback).

THE LIVE LONGER NOW COOKBOOK FOR JOYFUL HEALTH & LONG LIFE—Jon N. Leonard and Elaine Taylor. Grosset & Dunlap, Inc., 51 Madison Avenue, New York City (10010), 1977. 368 pages, $12.95.

LUPUS: THE BODY AGAINST ITSELF—Sheldon Paul Blau, MD, Director of the Division of Rheumatic Diseases at Nassau County Medical Center and Associate Professor of Clinical Medicine, School of Medicine, State University of New York at Stony Brook; and Dodi Schultz, Science Writer. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1977. 112 pages, $5.95.

MAN AT HIGH ALTITUDE—The Pathophysiology of Acclimatization and Adaptation—Donald Heath, MD(Sheffield), PhD(Birmingham), FRCP, FRCPath, George Holt Professor of Pathology, University of Liverpool; and David Reid Williams, Department of Pathology, University of Liverpool. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th Street, New York City (10036), 1977. 292 pages, $28.00.

THE MULTIPLE SCLEROSIS DIET BOOK—Roy L. Swank, MD, PhD, Professor Emeritus, Department of Neurology; and Mary Helen Pullen, Administrative Assistant, Department of Neurology, University of Oregon Health Sciences Center, Portland. Doubleday & Company, Inc., 245 Park Avenue, New York, NY (10017), 1977. 326 pages, $8.95.

THE NEW NUTS AMONG THE BERRIES—Ronald M. Deutsch. Bull Publishing Co., P.O. Box 208, Palo Alto, CA (94302), 1977. 359 pages, $8.95 (cloth), $4.95 (paper).

OUTLINE OF ORTHOPAEDICS—Eighth Edition—John Crawford Adams, MD(Lond), MS(Lond), FRCS(England), Consultant Orthopaedic Surgeon, St. Mary's Hospital, London; Civil Consultant in Orthopaedic Surgery, Royal Air Force; Production Editor, **Journal of Bone and Joint Surgery.** Longman Inc., 19 West 44th Street, New York City (10036), 1976. 472 pages, $13.50 (paperback).

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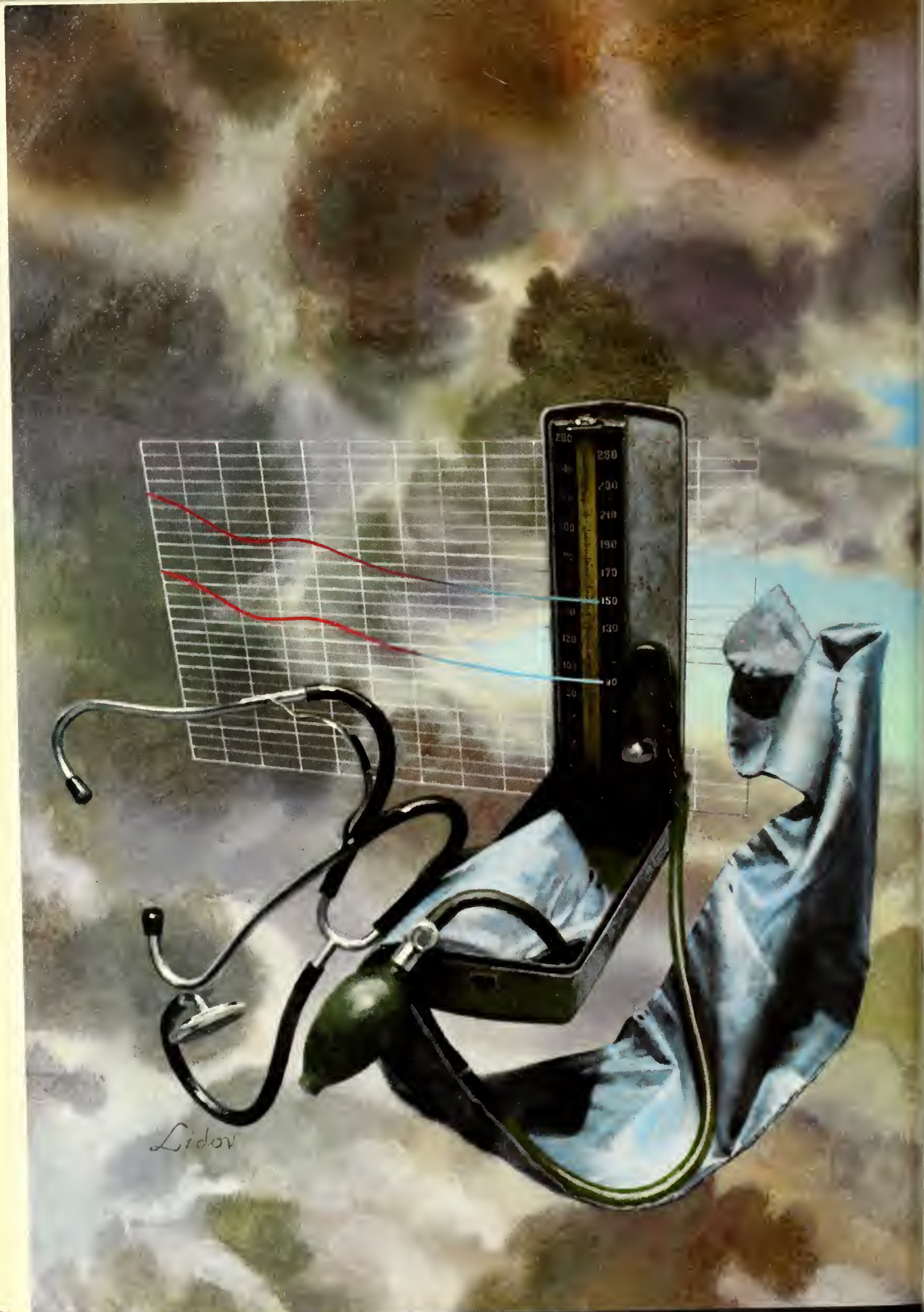
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References:

1 Dornfeld L, Kane R: Metolazone in essential hypertension: The long-term clinical efficacy of a new diuretic. *Curr Ther Res* **18**:527-533, 1975.

2 Cangiano JL: Effects of prolonged administration of metolazone in the treatment of essential hypertension. *Curr Ther Res* **20**:745-750, 1976.

3 Data on file: Medical Department, Pennwalt Prescription Products.

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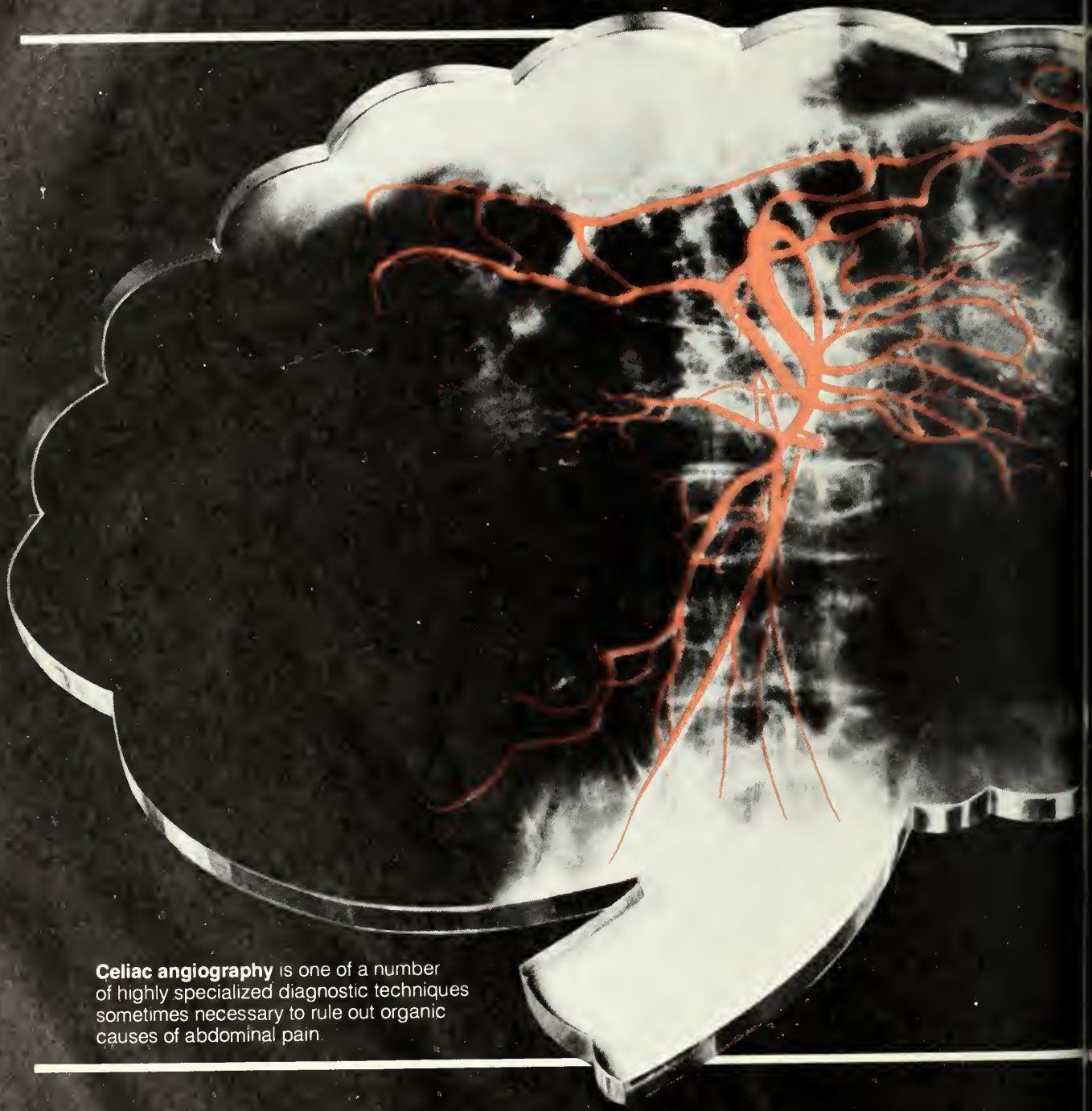

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Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude development of ataxia, oversedation or confusion (not more than two capsules per day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacologic effects of agents, particularly potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

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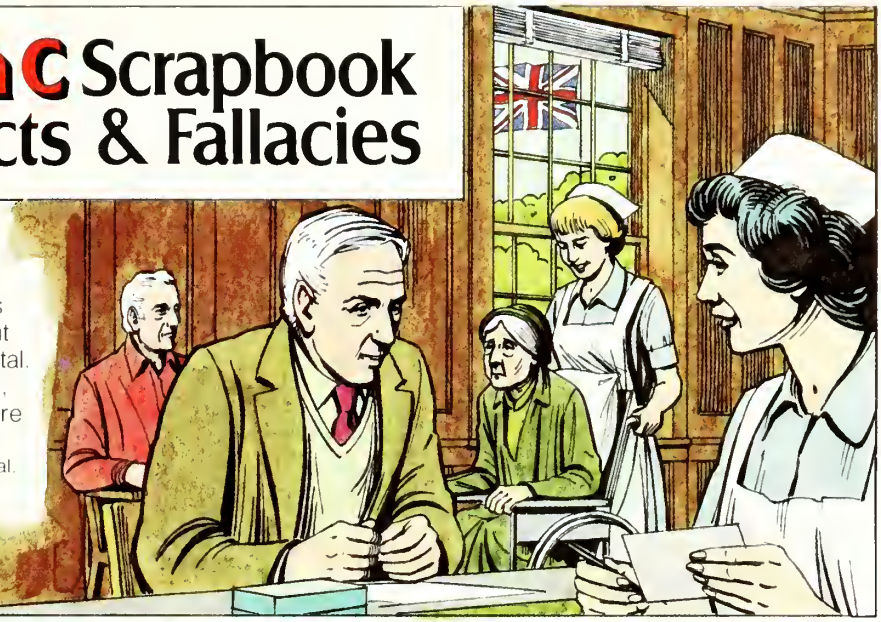

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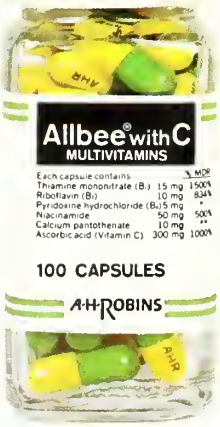

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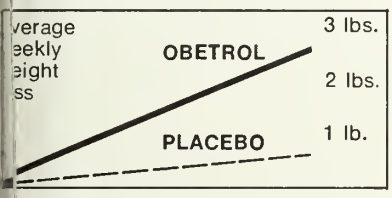

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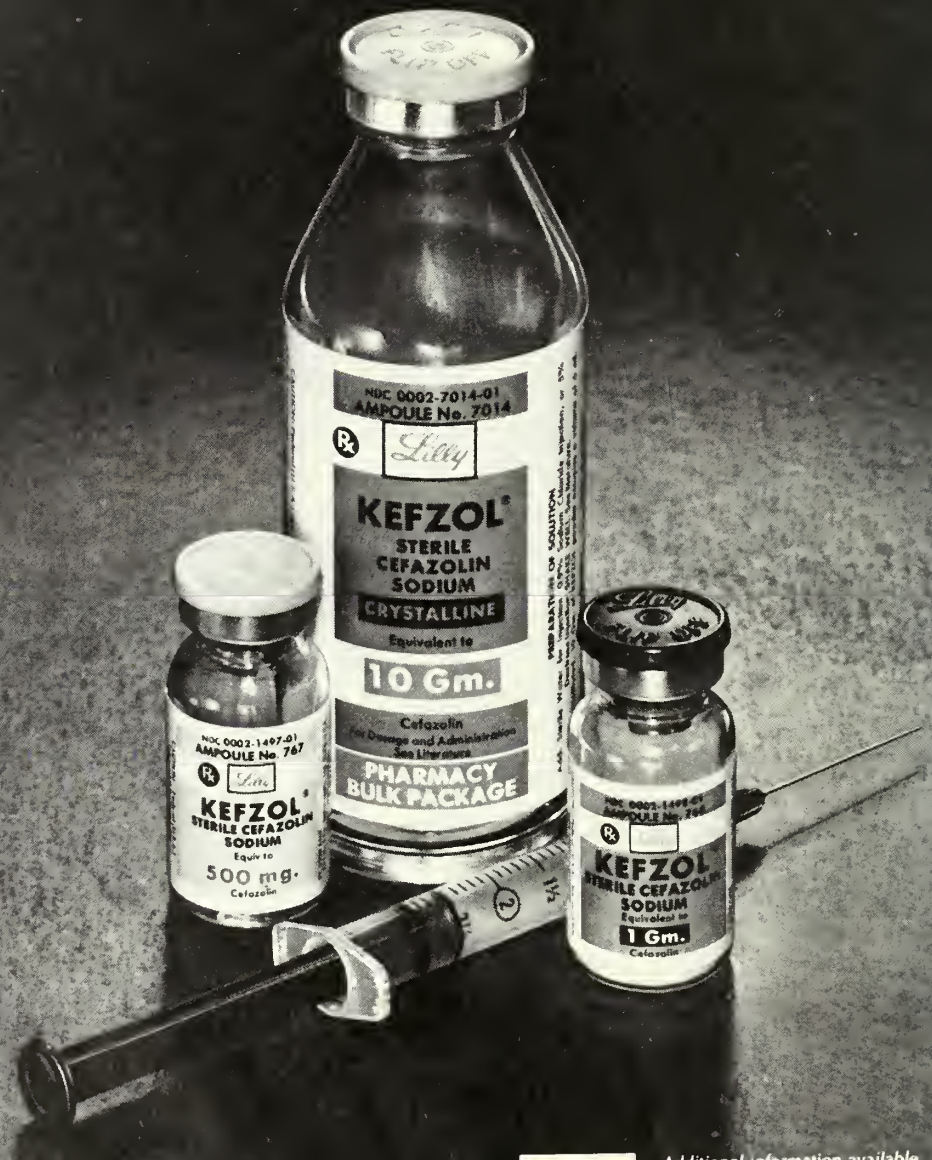

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Refer to: Rapport RL II, Ojemann GA, Wyler AR, et al: Surgical management of epilepsy. West J Med 127:185-189, Sep 1977

Surgical Management of Epilepsy

RICHARD L. RAPPORT II, MD; GEORGE A. OJEMANN, MD; ALLEN R. WYLER, MD, *and* ARTHUR A. WARD, JR., MD, *Seattle*

Therapy with anticonvulsant drugs reduces the frequency and severity of seizures in many but not all epileptic patients. Unfortunately, in a significant number control remains poor even when maximal doses of multiple anticonvulsant drugs are given. Some of these patients are candidates for surgical treatment of epilepsy. The operative management of convulsive disorders is a well-established technique and is available in some centers. In selected cases, such operations are both safe and effective, with good long-term improvement or complete control in 76 percent of patients. We have summarized the 24-year experience with surgical operation for epilepsy at the University of Washington Medical Center.

MANAGEMENT OF CONVULSIVE DISORDERS continues to be a vexing problem even with the introduction of effective anticonvulsant drugs. A reasonable figure for the prevalence of epilepsy (when prevalence is based on two or more afebrile seizures) is about five to seven per 1,000.[1,2] It is widely reported anecdotally that most of these cases are controlled on medication. Seizure control, however, is a subjective judgment and its definition is dependent on many variables which include patient reporting and physician interpretation. Reynolds has critically reviewed several published series concerned with the adequacy of seizure control in patients receiving anticonvulsant drugs; these data indicate that in only 30 to 37 percent of all types of seizure disorders are patients seizure free because of medication over a two-year follow-up period.[1] At the end of ten years only 10 percent of all patients had remained seizure-free. There are subpopulations that do significantly better, and an occasional seizure may be tolerable for certain patients, but careful epidemiologic studies do not support the contention that seizures in most epileptic patients are completely controlled by medications. Furthermore, chronic anticonvulsant medications are not without serious side effects. The problems of Purkinje cell loss and cerebellar ataxia, abnormal folate metabolism, hematologic toxicity, sedation, psychotic reactions, abnormalities of connective tissue, endocrine effects and so-called allergic hypersensitivity have all been reviewed in detail.[3] Furthermore, in approximately 20 to 30 percent of epileptic patients, seizures are uncontrolled by any standard with current anticonvulsant medications, even with careful monitoring of serum drug levels. In patients with seizures of focal origin, particularly temporal lobe foci, control is espe-

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Submitted February 7, 1977.

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cially difficult to achieve. In some patients in whom seizures are not fully controlled by anticonvulsant medications, surgical operation is a treatment option. Robb has conservatively estimated that 10 percent of all patients with seizures, or roughly 105,000 people in the Unitel States, may be candidates for epilepsy operations.[2]

Epilepsy has been surgically treated since the first Stone Age trephinations. The long and often colorful history of operations for seizure control includes blood-letting, fenestration of the dura, cervical sympathectomy, muscle-to-brain grafts, adrenalectomy, clitoridectomy and bowel resection; these have been reviewed by Marshall.[4] The modern era for both the medical and surgical treatment of the epilepsies began in the mid-19th century with the work of Fritsch and Hitzig, Hughlings Jackson, Gowers and later Horsley. These pioneers in the study of the central nervous system described not only the various clinical presentations of seizures, but also cortical stimulation and localization experiments which began to focus on abnormal neuronal mechanisms as causing epilepsy. With this background, Horsley and then Foerster first described subpial cortical resections for the control of seizures. Following the advent of modern electroencephalography and anesthesia, Penfield and his students developed the modern techniques for epilepsy operations. This paper discusses the rationale for this procedure, methods of patient selection, and the long-term results of surgical therapy for epilepsy at the University of Washington Medical Center over the past 24 years.

Patient Selection

The criteria for selection of patients as operative candidates have been made standard. Such patients must have intractable seizures which are refractory to adequate medical therapy; the epileptic focus generating the seizures must be identified; this focus must be in dispensible cortex. The first criterion is the most important and a thorough attempt must be made to control the seizures with anticonvulsant drugs. A trial of standard doses of diphenylhydantoin (Dilantin®) alone is insufficient. The focus is localized initially by obtaining a careful description of a typical seizure. These data should be confirmed by detailed electroencephalographic (EEG) localization. Findings on contrast studies (usually angiography and pneumoencephalography) should be consistent with the final formulation of the problem. Finally, this focus must be located in a part of the cortex which can be surgically removed without significant neurological deficit. Therefore, a patient is not a candidate for surgical therapy if the focus is located in primary speech cortex.

For patients in whom medical therapy has failed, evaluation begins with routine history (and family history), examination, detailed description and preferably observation of a typical attack, as well as basic EEG studies including sleep tracings. Next the patient is admitted to hospital for more detailed diagnostic studies. These commonly include pneumoencephalography, computerized axial tomography, special localizing EEG studies and neuropsychological testing. Angiography including lateralization of speech by the Wada test (intraarterial ultra-short-acting barbiturate) may also be done. If an obvious structural lesion can be found (neoplasm, arteriovenous malformation [AVM]), the appropriate operation can be undertaken. If the seizure focus can be discretely localized to one area on one side of the brain in nonessential cortex the patient should be considered for surgical treatment.

This approach to the treatment of focal epilepsy is based on current theoretical models of epileptogenic neurons as reviewed by Ward.[5] The concept is fundamentally simple: to remove that aggregate of abnormal neurons that are responsible for the ictus while sparing vital parts of the brain. A number of observations suggest that effective resections depend on other variables also. For example, temporal lobe resection is more likely to result in long-term benefit when the medial temporal structures (especially hippocampus) are included. On the other hand, success does not seem to depend on removal of insular cortex even if found to be abnormal on direct recording. The collected results of epilepsy operations in highly selected populations of medically intractable disorders are uniformly good in many reported series, with approximately 75 percent of patients seizure free or significantly improved postoperatively.[6,9,10]

University of Washington Series

The data presented here are based on a review of the records of 45 patients (47 operations) treated by three surgeons between 1952 and 1976. There have been no operative deaths; in one patient a craniotomy was done but no abnormal focus was noted at the time of electro-

TABLE 1.—*Age in Years at the Time of Seizure Onset and at the Time of Epilepsy Operation*

	Age (Operation)	*Age (Onset)*
Mean in years	26.6	12.1
Range in years	7-47	1-43
Number of cases by decades		
0-9	0	21
10-19	10	15
20-29	23	6
30-39	11	1
40-49	4	1

TABLE 2.—*Type of Seizures*

	Primary	*Secondary*
Major motor	9	18
Complex partial	25	2
Focal	7	2
Secondarily generalized	0	5
Absence	1	3
Akinetic	1	1
Other	2	3

TABLE 3.—*Resection Site*

	Left	*Right*	*Total*
Frontal	1	8	9
Temporal	14	17	31
Partial	1	2	3
Hemispherectomy	1	0	1
Temporoparietal	0	1	1
Frontoparietal	1	0	1
No resection	1	0	1

corticography and therefore no tissue was resected. The age of onset of seizures in this population is shown in Table 1. In 81 percent of our patients, seizures began before the age of 20; this figure is in close agreement with those in other large series.[7,8] The age distribution at the time of operation is also shown in Table 1 and likewise corresponds with published data.[8] The duration of our follow-up on these 45 patients averages 4.4 years and ranges between ten weeks and 20 years.

Complex partial seizures (also called temporal lobe or psychomotor epilepsy) constituted the majority of the types of attacks in our series (Table 2). Major motor (grand mal) and focal motor or sensory seizures were the next most common. Major motor and secondarily generalized seizures were the most common secondary types of attacks. As shown in Table 3, the temporal lobe was the most common resection site.

Our results over 24 years are very similar to those reported in the other major series with similar selection criteria.[6,9,10] As shown in Table 4, 36 percent of all patients were seizure-free for

TABLE 4.—*Results*

	Seizure Free	*Improved*	*Unchanged*	*Total*	*Percent*
Frontal	2	5	2	9	15
Temporal	13	13	4	30	64
Parietal	0	0	2	2	21
Hemispherectomy	1	0	0	1	
Temporoparietal	0	1	0	1	
Frontoparietal	1	0	2	3	
No resection	0	0	1	1	
Total	17	19	11	47	
Percent	36	40	24		
	76				

the period of follow-up (excluding the immediate postoperative period); an additional 40 percent were improved. Improvement is defined as a reduction in the seizure frequency of such a magnitude that there was a major beneficial impact on the patient's life. In practice, this usually implied a decrease in seizure frequency of 50 percent or more; often only occasional seizures were reported. Therefore, 76 percent of patients were seizure-free or significantly improved, while 24 percent (11 patients) showed no improvement. These figures are in close agreement with those reported by Rasmussen in 1974 based on 629 cases.[10]

In 36 percent of our patients in whom temporal lobe resection was done, there also was a psychiatric diagnosis. Those patients with complex partial seizures and no psychiatric diagnosis had a good result in 95 percent of cases compared with a good result in 70 percent of cases when psychiatric problems were diagnosed. The problem of complex partial seizures concomitant with psychiatric disturbance is, of course, one of the major variables which complicate interpretation of this kind of data. Of the two patients operated upon twice, one improved following the second procedure; both had psychiatric diagnoses as did the patient in whom craniotomy was done but no resection. The latter was unchanged postoperatively.

The light microscopic pathological findings in 36 cases of tissue removed at epilepsy operation are summarized in Table 5. Gliosis of both cortex and deep nuclei predominated, followed by neuronal loss and satellitosis—all nonspecific changes. Four tumors were reported. Some of the epileptic tissue has also been examined biochemically and a decrease in sodium, potassium

TABLE 5.—*Pathology (n=36)*

	Temporal	*Frontal*	*Parietal*	*Hemispherectomy*	*Total*
Gliosis (white)	12	3	..	..	15
Gliosis (grey)	5	1	1	..	7
Gliosis (deep)	9	..	..	..	9
Neuronal loss (grey)	4	2	..	..	6
Neuronal loss (deep)	5	..	..	..	5
Satellitosis	3	1	1	..	5
Edema	1	..	..	..	1
Atrophy	2	..	..	..	2
Cicatrix	2	..	..	..	2
Calcification	2	2	..	..	4
Necrosis	1	..	..	1	2
Neuronal pyknosis	3	..	..	..	3
Cystic	4	1	..	..	5
Hemosiderin	4	1	..	..	5
Glioma, grade 1	1	..	..	..	1
Oligodendroglioma	..	2	..	..	2
Meningioma	..	1	..	..	1
AVM	1	..	..	..	1
Angioma	1	..	1	..	2
Status marmoratus	..	..	1	..	1
No diagnostic alteration	5	2	..	..	7

AVM = arteriovenous malformation

TABLE 6.—*Probable Etiological Events*

Head injury	11
Porencephaly	2
Encephalitis	2
Abscess	1
Dermoid	2
Tumor	4
AVM/Angioma	3
Perinatal disease	6

AVM = arteriovenous malformation

adenosinetriphosphatase (ATPase) activity has been recently reported.[11] This enzyme system is felt to be at least in part responsible for maintaining the ionic gradient across bioactive membranes. A summary of more probable gross causes in 31 of the 45 cases is shown in Table 6.

Discussion

Modern surgical resection for the treatment of medically intractable epilepsy is a somewhat neglected but valuable adjunctive form of therapy. The goals and risks of this procedure in a highly selected population are well documented.[6,10] Patients are candidates (1) in whom adequate control is not achieved with anticonvulsant drugs or who, because of toxicity or idiosyncratic reaction, are unable to take the appropriate medication and (2) in whom there is a localizable lesion in nonessential cortex. Other considerations are the presence of additional neurologic disability such as mental retardation or psychiatric illness. While fixed deficits such as retardation will not be improved, there is evidence that seizure control may alter some behavioral abnormalities. It is an especially common observation that patients with temporal lobe seizures are behaviorally improved postoperatively.[6,13] A final important consideration is the patient's motivation and ability to tolerate the rigors of both the evaluation for surgical operation and craniotomy under local anesthesia.

Because corticographic localization of electrical abnormality is essential to maximize the beneficial results of surgical therapy for epilepsy, general anesthesia is seldom used. This, of course, does not apply in children. The operation is usually done with some sedation and local anesthetic. This arrangement is, obviously, a major stress for the patient. Our experience has been that the motivation for cure or improvement is great enough that the procedures are tolerable for the patients we select.

Since local anesthetic is used, the risk of general anesthesia is obviated. The remaining unlikely risks are intraoperative catastrophe (such as vascular occlusion) or postoperative complications such as wound infection, pulmonary embolus or pneumonia. The final risk is that the procedure will fail to improve seizure control.

Our results are similar to most other series in reporting a success rate of approximately 75 percent when success is defined as no or fewer seizures when medication is given.[6,9,10] Our practice has been to maintain the preoperative medications for at least one year following the procedure. If at that time no seizures have occurred the drugs may be stopped. Under this protocol, 36 percent of the patients in this series are seizure free and an additional 40 percent are significantly improved. These figures are so encouraging that it is surprising that more operations for intractable seizures are not done.

The University of Washington is one of the few centers routinely carrying out surgical operations for epilepsy, yet only 50 epileptic patients have been operated upon in 24 years. Why should this be the case? Several reasons may be listed: (1) ignorance of the operation's availability, (2) expense, (3) patient fear, (4) reluctance of primary doctors to suggest an operation when many

anticonvulsants are available. We believe that surgical treatment can make a major beneficial impact on the lives of properly selected patients; the complication rate is low and the results usually good or excellent.

Because of the suggested relationship between seizures and behavioral disorders, consideration should also be given to the timing of epilepsy operations. The lives of patients with intractable seizures are profoundly influenced not only by the ictal events, but also by the continual threat of seizures. Moreover, even in the absence of specific intellectual deficits, a child with continually abnormal electrical activity may be retarded in learning simply on the basis of time available to learn. They may also be retarded in their social interactions both in school and at home. Behavioral disturbances and dependence are common concomitants of intractable epilepsy. For these reasons, early consideration should be given to surgical operation when aggressive medical management has failed. Table 1 shows that the mean age at operation in our series was delayed 14.5 years beyond the mean age of seizure onset. The final results in terms of both seizure control and improved interpersonal relationships may be favorably influenced by early surgical intervention.

Finally, it should be noted that a variety of surgical techniques other than cortical resection have been proposed. Some of these, including stereotaxic lesions in several deep targets, are encouraging. The most promising are radiofrequency lesions in the medial temporal lobe including amygdala, hippocampus and fornix.[12] More recently cerebellar stimulation has been advocated, but the possible benefits of this technique remain both theoretically and practically conjectural.

Summary

The theoretical basis and history of surgical treatment of epilepsy have been briefly reviewed. The limits of medical management of seizures are discussed, and criteria for patient selection as surgical candidates are summarized. While operations for epilepsy are done infrequently at most centers, those neurosurgical units with a major commitment in this area do a significant number of such operations. The process of patient selection includes multiple EEG's, angiography, speech localization, pneumoencephalography or computed tomography (CT) scanning and neuropsychological testing. Those patients with focal seizure disorders which do not involve vital structures (such as primary speech cortex) should be considered for epilepsy surgery.

The data presented are based on a review of the records of 45 patients in whom a total of 47 operations were done in the past 24 years; there were no deaths. Of these patients, 76 percent are seizure-free or improved for the follow-up period, which averages 4.4 years. Pathological findings in resected tissue are nonspecific in most cases. However, four brain tumors, two angiomas and one AVM were included in the series.

Finally, those patients with focal seizures in whom medical management fails or in whom complications of drug therapy develop might be given earlier consideration as surgical candidates.

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Refer to: Reynolds RD, Greenberg BR, Hill R, et al: Survival in lung cancer. West J Med 127:190-194, Sep 1977

Survival in Lung Cancer

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Analysis was carried out according to stage and tissue type of 392 consecutive cases of lung cancer diagnosed at David Grant Medical Center between 1960 and 1974. Biphasic survival curves were described with a variable primary phase and a constant (1.1 percent per month) secondary phase. Survival was found to correlate both to histology and stage. The best survival was found in stage I bronchoalveolar carcinoma. Even in the more favorable categories a leveling off of survival was not found. This study strongly suggests that surgical treatment of lung cancer, while beneficial, cannot expect to be considered as a curative procedure in more than 10 percent of cases. Radiotherapy did not prolong survival.

THE SURVIVAL in lung cancer is known to be dismal.[3-8] Factors such as histologic type and extent of disease are recognized as being significant factors in the determination of survival.[2,7] Most cases of lung cancer are unresectable at the time of diagnosis and fall into the category of stage III under the accepted classification by the American Joint Committee on Cancer Staging and End Results Reporting.[2]

The current study compares the survival in each of the histologic types and clinical stage. In addition, a fourth stage was devised to indicate those patients with extrathoracic metastasis at the time of diagnosis.

Methods

Clinical records, tumor board files and histologic material of 403 consecutive cases of carcinoma of the lung diagnosed at David Grant Medical Center between 1960 and 1974 were reviewed. Eleven were eliminated because of lack of histologic material for review or because of lack of followup data.

The cases were analyzed according to the histologic type and classified in one of six groups: epidermoid, adenocarcinoma, undifferentiated small (oat) cell, anaplastic large cell, bronchoalveolar and nonclassifiable anaplastic carcinoma. Each histologic cell type was classified according to stage. In an attempt to separate the large number of those with stage III disease, an arbitrary division was made according to the presence or absence of extrathoracic disease at the time of diagnosis. Those with extrathoracic disease were classified as stage IV. Survival curves were calculated by the actuarial method; that is, the number living compared with the number at risk.

When the survival curves for adenocarcinoma and epidermoid carcinoma were analyzed according to stage, a biphasic slope of the curve was noted. Estimates of the rates of death per month were then made based on the calculation of the slope of each curve. This was done in order to provide some degree of prognosis and predictability without waiting for completion of the end results reporting.

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Submitted January 5, 1977.

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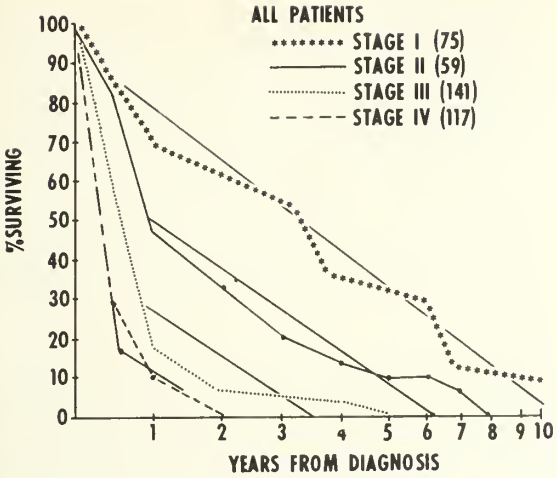

Figure 1.—Survival in 392 cases of lung cancer by stage. The slopes of all curves can be seen to have rapid primary and a constant secondary characteristic.

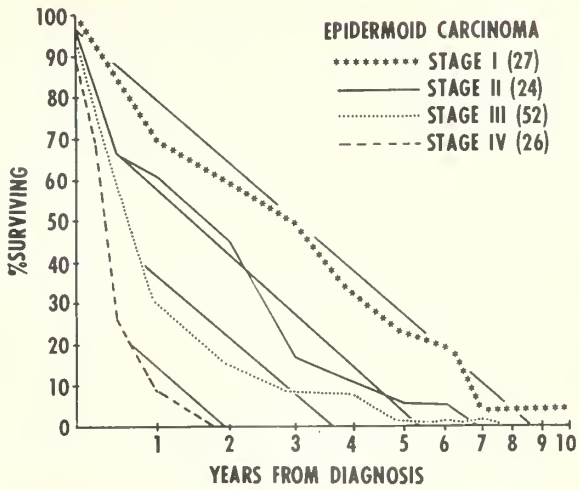

Figure 2.—Survival in 129 cases of epidermoid carcinoma of the lung by stage. The initial slope of the mortality curve varies by stage while the secondary stage is constant.

Results

The number of cases with each histologic pattern and stage of disease is shown in Table 1. Epidermoid carcinoma was less likely to present with extrathoracic disease than adenocarcinoma or large cell carcinoma. Oat cell carcinoma and nonclassifiable undifferentiated carcinoma were more likely to present with advanced (stage III or IV) disease than the other tissue types. Bronchoalveolar was more likely to present as stage I disease. Squamous cell carcinoma was more likely to be resectable than adenocarinoma, large cell or oat cell carcinoma.

Analysis of all patients (Figure 1) by stage, regardless of the cell type, showed a median survival of 38.2 months for stage I, 11.0 months for stage II, 7.3 months for stage III and 4.4 months for stage IV disease. After eight months the death rate was 1.1 percent per month in stage I cases. Before this period, the rate was 2.4 percent. For stage II disease, the initial death rate was 4.5 percent per month for 11 months and with a fall to 1.0 percent after 11 months. For stage III, the rate was 7.0 percent per month for ten months and 1.1 thereafter. In stage IV, the primary death rate was 11.9 percent per month for seven months, falling to 1.0 percent after seven months. It should be noted that the secondary death rates were almost identical regardless of the stage of disease.

Analysis of epidermoid carcinoma survival by stage showed a distinct difference between each stage (Figure 2). Median survival for stage I was 33.9 months; for stage II, 21.3 months; for stage III, 8.2 months, and for stage IV, 3.2 months. The death rate was fairly constant in stage I disease after six months and was calculated to be 1.1 percent per month. The death rate for the first six months was 2.5 percent per month. The initial death rate had a greater impact on survival statistics with advancing stage. The death rate for the first six months in stage II disease was 5.5 percent per month and was 1.1 percent thereafter. The slope of the second portion of the survival curve was similar, therefore, to that

TABLE 1.—*Numerical Listing of Cases of Lung Cancer by Stage and Histologic Type*

	Squamous Cell Carcinoma	*Adeno-carcinoma*	*Oat Cell Carcinoma*	*Large Cell Carcinoma*	*Broncho-alveolar Carcinoma*	*Anaplastic NOC Carcinoma*	*Total*
Stage I	27	15	4	10	16	3	75
Stage II	24	16	8	7	4	0	59
Stage III	52	29	32	11	6	11	141
Stage IV	26	33	23	12	3	20	117
Total	129	93	67	40	29	34	392

NOC = not otherwise classifiable

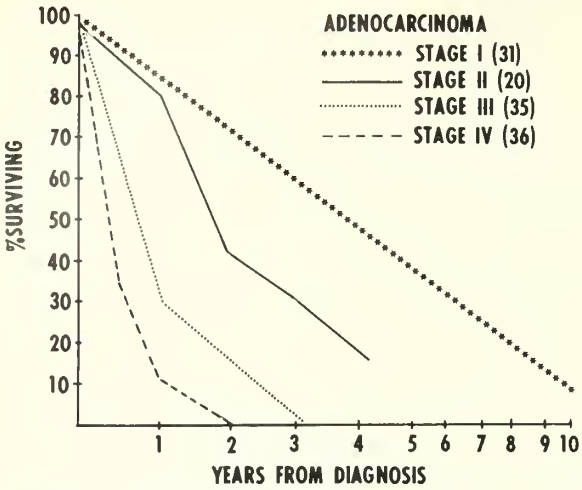

Figure 3.—Survival in 122 cases of adenocarcinoma, including bronchoalveolar, by stage. A constant secondary mortality rate is again seen.

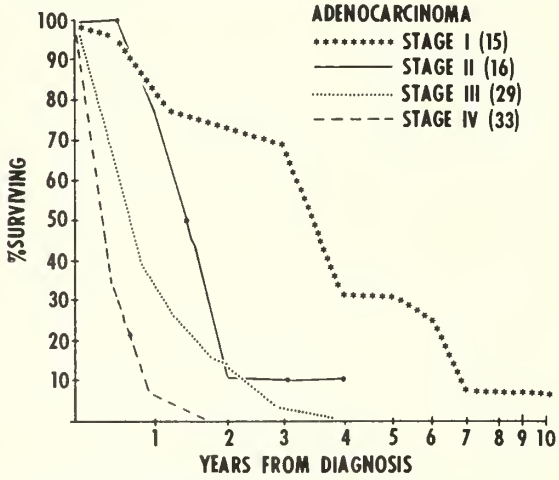

Figure 4.—Survival in 93 cases of adenocarcinoma, excluding bronchoalveolar, by stage.

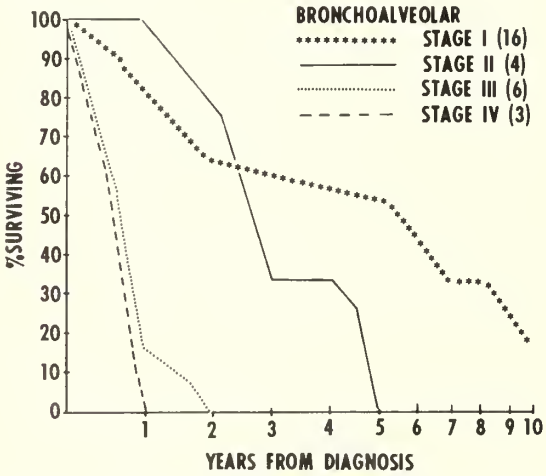

Figure 5.—Survival in 29 cases of bronchoalveolar carcinoma by stage showing the poor survival in advanced disease.

found in stage I disease. Further analysis showed that this portion of the curve was similar for each stage of the disease. Survival therefore becomes an inverse factor of the slope and the duration of the initial portion of the survival curve. For stage III disease the initial mortality rate was six percent per month and for stage IV disease it was 12.5 percent per month. In each stage, the initial fall in survival was completed within ten months and the death rate then became similar regardless of stage.

When adenocarcinoma and bronchoalveolar carcinoma were considered as a single group (Figure 3), the median survival for stage I was 32.2 months; for stage II, 21.5 months; for stage III, 8.9 months, and for stage IV, 4.7 months. The death rate in stage I disease was 1.1 percent per month. The mortality rate, for the first 24 months, in stage II adenocarcinoma was 2.5 percent per month. The rate then declined to 1.0 percent per month. The initial morality rate in stage III disease, as measured over the first 12 months, was 5.8 percent per month before declining to 1.1 percent per month. For stage IV disease, the death rate was 7.5 percent per month for the first 12 months before appearing to drop off to the lesser rate. Since the number of persons with stage III or IV disease surviving the initial death rate is small, the value of the second, or uniform, death rate is only important because of the comparison with lesser stages of disease.

Analysis of the adenocarcinoma group, when bronchoalveolar cases have been excluded, is shown in Figure 4. The survival curves are less well defined than those seen in the previous groups. The median survival of stage I disease was 41.7 months; for stage II disease, 17.2 months; for stage III disease, 8.1 months, and for stage IV disease, 3.3 months. The calculated death rate was 1.2 percent per month in stage I adenocarcinoma. The initial death rate in stage II disease was 3.7 percent per month; for stage III disease, 5.5 percent, and for stage IV disease, 8.3 percent.

Separate analysis of bronchoalveolar carcinoma, (Figure 5) showed a median survival for stage I disease to be 66 months while the median survival for stage II was 28.7 months; for stage III, 8.0 months, and for stage IV disease, it was 6.6 months.

The median survival in large cell undifferentiated carcinoma was 20.5 months for stage I, 8.3 months for stage II, 5.2 months for stage III and 1.3 months for stage IV disease (Figure 6).

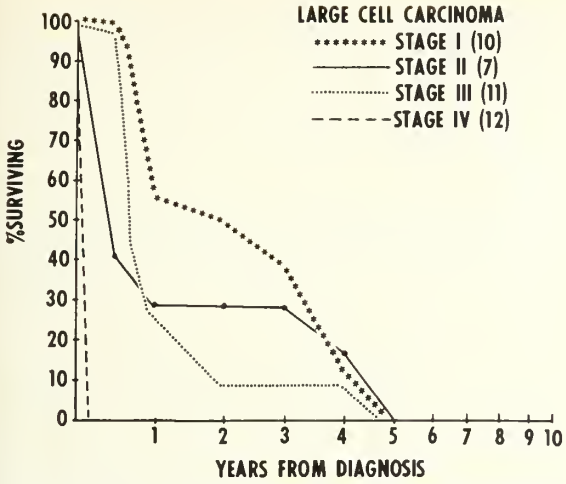

Figure 6.—Survival by stage in 40 cases of large cell carcinoma of the lung.

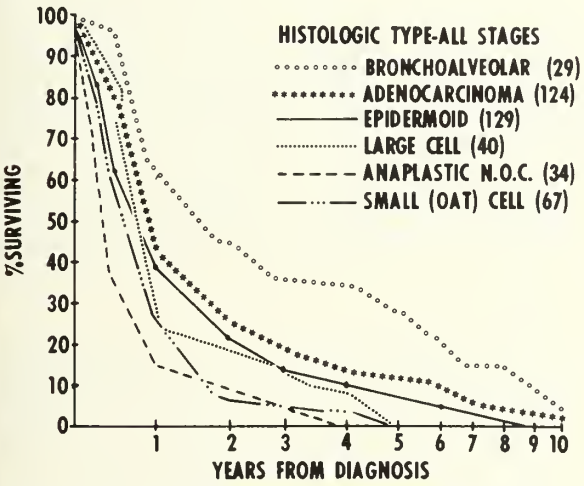

Figure 7.—Survival in 392 cases of lung cancer by histologic types. The median survival exceeded 12 months in only bronchoalveolar carcinoma, a reflection of the predominance of stages I and II disease in this disorder.

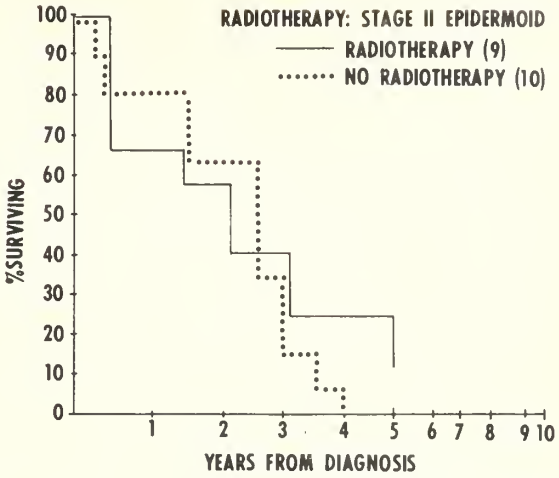

Figure 8.—Survival in stage II epidermoid carcinoma as influenced by radiotherapy. No beneficial effect on survival was found.

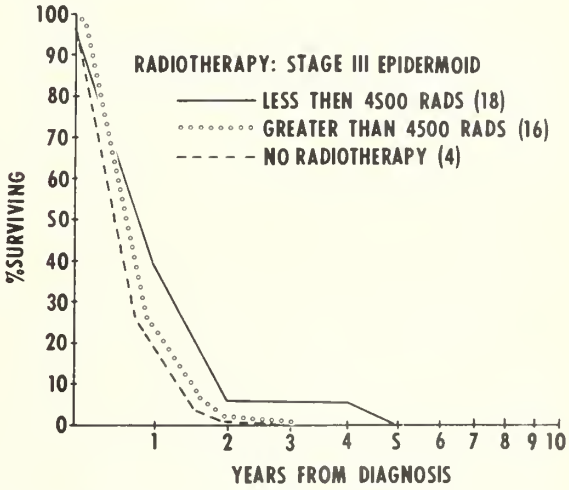

Figure 9.—Survival in 38 cases of stage III epidermoid carcinoma according to radiation dose. No beneficial effect on survival could be shown.

The median survival for both stage I and II oat cell carcinoma was 7.4 months. With a total of only 12 cases in this combined category, no difference could be found between the two stages. The median survival in stages III and IV also failed to show any separation (7.4 months).

Evaluation by histology without regard to stage (Figure 7) fails to show clear divisions in the slopes of the survival curves. While survival in bronchoalveolar carcinoma is superior to the other histologic categories, this advantage was less pronounced than was anticipated before this study. The survival curve suggests that the improved survival is related to early detection with regard to clinical stage rather than to a relatively benign nature of the disease process. The high proportion of stage I disease mentioned earlier is probably a manifestation of the more common peripheral location and slow doubling time in this tumor type. The median survival of the bronchoalveolar carcinoma cases in this series was only 18.0 months. By comparison, the median survival in adenocarcinoma, large cell, epidermoid, oat cell and anaplastic not otherwise classifiable (NOC) carcinomas was 11.0, 9.9, 8.5, 7.4 and 4.5 months respectively.

Both stage II and stage III cases of epidermoid carcinoma were evaluated for the effects of postoperative radiation therapy (Figure 8). In stage II disease, nine patients received radiation therapy and ten did not. The survival curve in this group of patients showed no advantage for using post-

operative radiotherapy. The median survival in the radiation treated group was 23.5 months and in the untreated group 30.7 months. It should be noted that there was no clear separation between the two groups. All patients in the untreated group had died at 48 months while two patients in the treated group lived beyond 48 months.

The cases of epidermoid carcinoma with stage III disease (Figure 9) were divisable into three groups: those who received no radiotherapy, those who received less than 4,500 rads to the involved field and those who received more than 4,500 rads. The median survival was calculated as 7.5 months in the untreated group, 8.5 months in the minimum treated group and 7.5 months in the full treatment group.

Discussion

This analysis of 392 consecutive cases of lung cancer diagnosed at a single institution gives a clear picture of the rapidly fatal nature of this disease. The breakdown of the classification into stages III and IV disease seems reasonable and is supported by the survival statistics in each of the histologic subtypes.

Comparison with reports in the literature shows that both the distribution of cases and survival are similar.[1,3,4,6-8] The biphasic nature of the survival curves has not been previously described. Discrepancies between survival in other reports[4] are felt to be attributable to the methods of reporting and the superiority of the maintenance of the institutional tumor registry as compared with large scale central registration of data. The negative value of postoperative radiation therapy has been previously described.[5]

The separation of each histologic type by stage has shown that the death rate may be described in two phases. The first, or primary phase, assumes the characteristic of the type and stage of the tumor. It was found to have increasing value with more advanced disease. On the other hand, the secondary death rate was found to be constant. The death rate during this secondary phase was found to be 1.1 percent per month in nearly all stages of these histologic categories.

The median survival was found to be related both to histologic type and to clinical stage. More meaningful data were obtained when both were analyzed together. The best median survival was found in stage I bronchoalveolar carcinoma (66 months). Stage I adenocarcinoma had a median survival of 41.7 months while epidermoid carcinoma was 33.9 months. The best median survival in stage II disease was also found in the bronchoalveolar group (28.7 months), while adenocarcinoma and epidermoid carcinoma had median survivals of 17.2 and 21.3 months, respectively.

The median survival in stage III disease was 8.2 months for epidermoid, 8.1 months for adenocarcinoma and 8.0 months for bronchoalveolar carcinoma. The median survival in stage IV disease was 6.6 months for bronchoalveolar carcinoma, 3.3 months for adenocarcinoma and 3.2 months for epidermoid carcinoma. Therefore, there appears to be a clear distinction between stages III and IV as determined by the extrathoracic metastsis. Mountain[7] previously described the difference in survival between those without distant metastasis (M_0) and those with distant metastasis (M_1), but did not make the differentiation within the advanced stages of lung cancer.

Oat cell carcinoma in this series was found to have a uniformly poor median survival (7.4 months) regardless of the stage at the time of presentation. These data suggest that oat cell carcinoma is frequently a systemic disease with metastasis commonly present at the time of diagnosis.

Analysis of those resected for cure (stages I and II) suggests that in few, if any, of the patients is surgical cure achieved. Though early detection and surgical resection remain both the treatment of choice and the most important factors in prolonging survival, it appears clear that in 10 percent or less can permanent cure by the surgical procedure be expected, even in the most favorable circumstances. Deaths continue to occur well beyond the five-year period postoperatively. More effective combined modality management of lung cancer is urgently needed.

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Refer to: Scheinhorn DJ, Angelillo VA: Antituberculous therapy in pregnancy—Risks to the fetus. West J Med 127: 195-198, Sep 1977

Antituberculous Therapy in Pregnancy

Risks to the Fetus

DAVID J. SCHEINHORN, MD, *and* VITO A. ANGELILLO, MD, *Salt Lake City*

A total of 1,939 reported births to mothers who received isoniazid ethambutol, rifampin and streptomycin alone or in combination, for all or part of their pregnancies, were surveyed to determine teratogenicity of these agents. There was no significant increase in birth defects with isoniazid, ethambutol and rifampin, in contrast to the use of streptomycin which was associated with mild auditory and vestibular defects. Guidelines for the treatment of active tuberculosis in pregnancy are therefore established.

THE MANAGEMENT of pulmonary tuberculosis is becoming more and more the responsibility of internists. A recurrent problem encountered is that of women who become pregnant while receiving antituberculous chemotherapy. The purpose of this report is to suggest guidelines for the management of such patients. To this end, the available data on teratogenicity of the four major antituberculous drugs (isoniazid [INH], ethambutol [EMB], rifampin [RMP] and streptomycin [SM]) are reviewed.

Results

Isoniazid

The widespread use of INH in both prophylaxis and treatment of tuberculosis has allowed the accumulation of a large body of data on its administration during pregnancy. The findings in 1,079 births to women who received the drug alone or in combination with other antituberculous medications, from ten series, are summarized in Table 1. The usual 300 mg per day dosage was administered in most of the studies.

Because of a possible effect on fertility in animals, large early studies examined the outcome of pregnancies in which either parent received INH alone.[1,2] During the first five years of observation, no significant differences were found between the INH and placebo groups in birth rates, sex ratios or birth weights. Specifically, there were no birth abnormalities recorded during the first year of follow-up; that is, in births to women who received INH throughout their pregnancy.

Lowe[3] in Wales compared the outcome of 71 pregnancies during which INH was administered and 167 pregnancies with no drug administration. The two birth defects (2.8 percent) in the INH group were a myelomeningocele in a female infant, and hypospadias in a male. The former infant was born to a mother who had two previous normal births after pregnancies throughout which she received INH. In the group which received no drugs, seven infants were found to have birth defects (4.1 percent).

Hammond and co-workers,[4] in studying the

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ABBEVIATIONS USED IN TEXT

EMB = ethambutol
IHN = isoniazid
RMP = rifampin
SM = streptomycin

TABLE 1.—*Isoniazid (INH) Administration During Pregnancy*

Authors	Births to Patients Receiving INH	Control Group	Birth Defects	
			Treated	Controls
Wilson et al[18] ..	8	..	0	..
Ludford et al[1] ..	26	35	0	0
Lowe, CR[3]	71	167	2	7
Hammond et al[4].	660	..	0	..
Jentgens, H[5]	300	432	3	0
Verbist et al[9] ...	4	..	0	..
Rocher et al[11] ..	5	..	0	..
Reimers, D[10] ...	1	..	0	..
Bobrowitz et al[6] ..	3	..	0	..
Place, VA[7]	1	..	0	..
TOTALS	1,079	640	5	7

possible carcinogenic effects of INH therapy, were able to trace 660 children exposed *in utero,* some to the age of 13 years. None had cancer. One was a mongoloid, and one was described as a "slow baby."

A large survey in Germany[5] compared the births to 2,051 women who received antituberculous chemotherapy during pregnancy with the births to 432 tuberculous women who were not treated while pregnant. There were no differences in birth defects between the two groups. In this study over 300 women received INH, with only three reported defects: a ventricular septal defect in one child, hammer toe in one and a deformed lower extremity in one.

Most other studies[6-11] involve smaller numbers, but with results similar to those above.

Ethambutol

Findings in live births to mothers after EMB administration during human pregnancy are summarized in Table 2. Lewit and associates[12] reported no signs of maldevelopment of the eye, nervous system or other organs in embryos up to 12 weeks gestation obtained from mothers who had received therapeutic dosages of EMB. The authors questioned whether EMB might have affected later morphofunctional differentiation.

In the report of Pyle,[13] four women received EMB during pregnancy, two throughout gestation.

TABLE 2.—*Ethambutol (EMB) Administration During Pregnancy*

Authors	Births to Patients Receiving EMB	Control Group	Birth Defects	
			Treated	Controls
Jentgens, H[5]	313	432	0	0
Wilson et al[18]	1	..	0	..
Marino et al[14] ...	1	..	0	..
Pyle, M[13]	4	..	0	..
Bobrowitz et al[6] ..	3	..	0	..
Place, VA[7]	1	..	0	..
Bobrowitz, ID[8] ..	42	..	8	..
Wilson, T[15]	1	..	0	..
Johnston, R[15]	1	..	0	..
Other*	2	..	0	..
TOTALS	369	432	8	0

*Unpublished data, Lederle Laboratories

All were delivered of healthy infants who developed normally, the oldest being five years of age at the last follow-up.

Bobrowitz[8] reviewed the medical records of all tuberculous pregnant patients over 11 years. In all, 38 patients had received EMB during some portion of their 42 pregnancies. Dosages ranged from 15 to 25 mg per kg of body weight. In 34 of the 42 children there were no defects at birth or in the follow-up period. In eight infants (19 percent), abnormalities were described, including supernumerary nipple, small umbilical hernia, withdrawal syndrome, mild right tibial torsion, congenital dislocation of the hip, left hydrocele, minimal metatarsus adductus, skin tags of the left fifth digit and two "strawberry marks." The author noted no pattern in these abnormalities nor increased incidence when compared with births to untreated mothers.

In the survey in Germany,[5] analysis of case histories of 182 women and of questionnaires completed by 131 women who had received EMB or RMP, or both, during pregnancy failed to show any evidence that either of these drugs had an embryotoxic effect.

Other published[6,7,14,15] and unpublished* reports involving EMB dosages of up to 25 mg per kg of body weight throughout or at various stages of pregnancy have not shown teratogenic effects of the drug.

Rifampin

Animal experiments with RMP in pregnancy yield conflicting results, depending on the species tested. Very high dosages (150 to 250 mg per kg of body weight per day) in rats and mice result

*Lederle Laboratories, Pearl River, N. Y.

in congenital malformations, primarily spina bifida and cleft palate.[16] Similar studies in rabbits produced no such defects.[17]

The number of patients reported after exposure to RMP in pregnancy has not been great, because of the relatively short time of the drug's availability, but the results of over 100 such cases are summarized in Table 3. In every trial except one,[9] the dosage was 600 mg per day. In one report two tuberculous women were unintentionally treated in the first trimester of pregnancy.[10] One bore a healthy child at term, and the other had a therapeutic abortion at five months gestation. Histological examination of the fetus showed no abnormality. The authors knew of 34 other cases in which no harmful effects of RMP administration during pregnancy were noted.

Eighty-four patients in the study in Germany[5] received RMP in combination with other antituberculous drugs with no adverse effects on their progeny. Rocher and co-workers[11] report five cases of normal children born to mothers treated with RMP during all or part of their pregnancy, including four who received the drug during the first trimester.

The small number of cases in other reports[9,18] show no teratogenic effects.

Streptomycin

Streptomycin crosses the placental barrier variably, with fetal levels reaching as high as 50% of the maternal concentration. Factors which influence this level include deficiencies of maternal excretion or detoxification, increased permeability of the placenta due to structural abnormalities, and other diseases of the mother or fetus.[19] Early animal experiments to establish definite auditory and vestibular toxicity in offspring after administration of SM during pregnancy have been inconclusive. In guinea pigs administration of SM in dosages comparable to human dosage failed to produce abnormalities in function or histologic abnormalities. Higher dosages, however, produced vestibular damage. In mice even massive SM dosage failed to produce damaged offspring, while in rats mild but definite damage was produced.[19]

The results of SM administration during pregnancy in humans in eight studies involving small numbers of patients are summarized in Table 4. A dosage of 1 gram per day was most commonly used, with total doses ranging from 10 to over 200 grams. While the testing itself is difficult in children, no neurosensory hearing defects of serious degree (that is, greater than 30 decibels in the speech frequencies) were observed.[19-21] Abnormalities were present, although rare, and were confined to the higher frequencies, without clinical disability. For example, one of 40 children in one study was found to have a high frequency loss and in two of 34 children, a vestibular defect was detected.[20] There was no observable effect of the function of these children in their daily activities. The numbers are too small for statistical comparison, but the authors note that age matched Helsinki school children not exposed to SM have 3.3 to 9 percent inner ear hearing loss, depending on testing method used.

TABLE 3.—*Rifampin (RMP) Administration During Pregnancy*

Authors	Births to Patients Receiving RMP	Control Group	Birth Defects	
			Treated	Controls
Wilson et al[18]	2	..	0	..
Jentgens, H[5]	84	432	0	0
Verbist, L[9]	4	..	0	..
Rocher, G[11]	5	..	0	..
Reimers, D[10]	1	..	0	..
Reimers, D[17]	5	..	0	..
TOTALS	101	432	0	0

Isolated cases of varying degrees of deafness have been reported[22] as well as one case of congenital deaf mutism.[23] No other types of birth defects in conjunction with the administration of SM during pregnancy are recorded.[2,18,22]

Discussion

It is a general principle that the administration of any drugs to a pregnant patient is to be avoided, because of possible fetal damage. However, when tuberculosis complicates pregnancy, prompt and adequate antituberculous chemotherapy is mandatory. Also, pregnancy may occur during the treatment of active pulmonary tuberculosis. Under such circumstances the risk to the developing fetus must be considered in advising the expectant mother and her obstetrician.

The outcome of the administration of INH, EMB and RMP to pregnant tuberculous women (1,549 births included in Tables 1 through 3) with most cases representing multiple drug therapy, points to the safety of these three drugs throughout pregnancy. The greatest number of patients received INH so that its use can be recommended with the least reservation. Although less voluminous, the data clearly support the safety of EMB and RMP administration during preg-

nancy. Careful monitoring of liver and ocular toxicity, as is usual with any tuberculous patient receiving these drugs, is also important in pregnant women.

The 390 births to patients who received SM (Table 4) produced children with clinically minor, but definitely present auditory or vestibular damage. There seems to be a significant risk of such damage to the fetus, although controls are lacking in most studies. We would recommend that as organogenesis of the inner ear occurs at around the seventh intrauterine week, and differentiation of the cochlear cells continues up to the halfway point of pregnancy,[19] avoidance of SM during this period is particularly important. Further, high single doses and treatment of pregnant women with impairment of renal function or toxemia might be particularly deleterious. Children whose mothers have received SM in pregnancy should be checked for auditory and vestibular disturbance as early as possible, since they may be especially vulnerable to further damage upon subsequent administration of SM and other aminoglycosides.

In conclusion, the risk to the fetus from administration of INH, EMB and RMP during pregnancy is small, and the use of these agents is not contraindicated. A strong two or three drug regimen is therefore available for the treatment of tuberculosis in pregnancy. Further, the use of SM in a patient known to be pregnant can easily be avoided. If SM is used in the treatment of a nonpregnant woman in her childbearing years, she should be warned of the risk of becoming pregnant. Finally, if SM therapy has been administered to a woman during the first half of her pregnancy, a decision regarding termination of the pregnancy might be considered. A fully informed patient would presumably take into account a host of personal factors, weighing heavily the fact that defects reported with SM administration are mild. It is to be hoped that the best possible antituberculous therapy, coupled with the best possible obstetric and social outcome, would be the result of such informed deliberation.

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TABLE 4.—*Streptomycin (SM) Administration During Pregnancy*

Authors	*Births to Patients Receiving SM*	*Control Group*	*Birth Defects*		*Births to patients receiving SM with:*		
			Treated	*Controls*	*High Frequency Hearing Loss*	*Vestibular Defect*	*Clinical Disability*
Wilson et al[18]	5	..	0	..			
Lowe, CR[3]	12	173	0	7			
Jentgens, H[5]	220	432	0	0			
Varpela et al[19]	51	..	0	..	6	0	0
Varpela et al[20]	40	..	0	..	1	2	0
Ganguin et al[21]	44	..	0	..	5	..	..
Khanna et al[23]	1	..	1	..	..	..	1
Conway N[22]	17	..	2	..	4	6	0
TOTALS	390	605	3	7	16	8	1

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Electrographic Exercise Stress Testing and Coronary Arteriography

Correlation Among 114 Men With Chest Pain

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The electrocardiographic response to exercise stress testing (EST) was compared with coronary arteriographic findings in 114 men referred for evaluation of chest pain. The men were divided into two groups: group A (69 men) in whom the coronary arteriograms showed at least one major vessel with greater than 70 percent reduction in cross sectional area, and group B (45 men) in whom there was no evidence of coronary arterial narrowing. In both groups A and B the description of chest pain was judged to be at least consistent with the diagnosis of angina pectoris if not always representing classical angina pectoris. Only men with a positive finding to EST and those with a negative EST response after achieving at least 90 percent of predicted maximum heart rate were included in the calculations. Our results were strikingly similar to those obtained from an extensive review of the literature and showed the following: sensitivity, 80.4 percent; specificity, 88.6 percent; predictive value of a positive test result, 91.1 percent; predictive value of a negative test result, 75.6 percent, and efficiency of the test 83.7 percent.

The maximal EST is a useful predictor of coronary artery disease when a male population is evaluated for chest pain. When a population is selected on some basis other than chest pain (such as elevated lipids or age), EST is a much less useful predictor of coronary artery disease.

CONTROVERSY CONTINUES regarding the clinical usefulness of electrocardiographic exercise stress testing (EST), and its value as a worthwhile tool for the diagnosis of coronary artery disease (CAD) has been seriously questioned. Recent articles in the literature have reported specific groups of patients in whom EST was found to be a poor predictor of CAD. These groups of patients include those with type II hyperlipoproteinemia,[1] asymptomatic men[2] and symptomatic women.[3]

In an effort to gain a better understanding of the clinical usefulness of EST as a predictor of CAD we reviewed our experience in 114 male patients with chest pain in whom treadmill EST and subsequent selective coronary arteriography were done. We found that in men without hypertension complaining of chest pain who were

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ABBREVIATIONS USED IN TEXT
CAD = coronary artery disease
ECG = electrocardiogram
EST = exercise stress testing
PMHR = predicted maximum heart rate

maximally exercised, the postexercise electrocardiographic response was a useful predictor of arteriographically demonstrable CAD.

Patients and Methods

Patients referred for evaluation of chest pain in whom EST and subsequent coronary arteriography were carried out were considered for inclusion in this study. Patients who were hypertensive, had valvular or myocardial disease, had had a previous myocardial infarction, had major resting electrocardiographic abnormalities or were receiving medications known to influence electrocardiographic repolarization were excluded.

Selective coronary arteriography was done using either the Sones or Judkins technique. The arteriograms were exposed on 35 mm film in multiple projections using a Philips 6″ Cesium Iodide Image Intensified System (Philips Medical Systems, Inc., Shelton, CT). The coronary arteriograms were evaluated by two independent observers without knowledge of the EST findings. CAD was judged as present if one or more major coronary vessels had an estimated luminal reduction in cross sectional area of at least 70 percent. Patients classified as normal had *no* suggestion of luminal narrowing in any vessel. Patients with CAD, but not 70 percent luminal narrowing in at least one major vessel, were excluded from the study.

In all, 114 men (mean age 44.6 years; range 23 to 65 years) were entered into the study on the basis of the above criteria, and were divided into two groups on the basis of the results of coronary arteriography. Group A comprised patients in whom coronary arteriograms showed at least one major vessel with greater than 70 percent reduction in cross sectional area. Group B comprised patients in whom there was no evidence of coronary arterial narrowing. In both groups A and B the description of chest pain was judged to be at least consistent with the diagnosis of angina pectoris, though not necessarily always representing classical angina pectoris, and served as the indication for coronary arteriography.

Exercise Stress Testing

Exercise testing was done with patients in the fasting state on a treadmill using the Bruce protocol.*[4] Our goal was to exercise each patient to the point of exhaustion. However, EST was discontinued if the patient complained of significant and limiting chest pain, shortness of breath, lightheadedness or dizziness, or if striking ST segment depression was noted. Standard 12-lead electrocardiograms (ECG) were done before, at 1-minute intervals during, and after the EST. The ECG's were recorded immediately and at 2-minute intervals after exercise for a total of at least eight minutes or until ST segment depression had returned to the resting state. The preexercise and postexercise ECG's were recorded in the supine

*EST according to the method of Bruce employs the principle of uninterrupted multistage treadmill exercise. Each stage lasts three minutes. There is a progressive increase in speed and grade as one moves through the stages.

TABLE 1.—*Exercise Test Results in 69 Men With CAD (Group A) Compared With 45 Men Without CAD (Group B)*

	Number		*Mean Age (years)*		*Chest pain during EST*		*Max HR Percent PMHR*		*Time on Treadmill (minutes)*	
	A	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*
Positive EST	41 (59%)	4 (9%)	48	39	88%	50%	137 (74%)	186 (99%)	5	10
Negative EST and 90% PMHR	10 (14%)	31 (69%)	42	40	30%	29%	176 (94%)	181 (93%)	10	10
Negative EST but less than 90% PMHR	12 (17%)	8 (18%)	50	38	92%	75%	138 (74%)	155 (82%)	6	10
Borderline EST and 90% PMHR	3 (4%)	2 (4%)	42	44	33%	100%	179 (95%)	175 (93%)	9	8
Borderline EST but less than 90% PMHR	3 (4%)	NONE	52		67%		128 (70%)		4	

CAD = Coronary artery disease
EST = Exercise stress testing
HR = Heart rate
PMHR = Predicted maximum heart rate

TABLE 2.—*Definitions of Statistical Terms*[12]

TP = True positive TN = True negative
FP = False positive FN = False negative

$$\text{Sensitivity} = \frac{TP}{TP+FN}$$

$$\text{Specificity} = \frac{TN}{TN+FP}$$

$$\text{Predictive value of positive test results} = \frac{TP}{TP+FP}$$

$$\text{Predictive value of negative test result} = \frac{TN}{TN+FN}$$

$$\text{Efficiency of test} = \frac{TP+TN}{TP+FP+TN+FN}$$

Incidence—Number of occurrences of a particular kind in any given period of a given population (for example, the incidence of poliomyelitis in Transylvania during 1967 was 4 cases per 100,000 population).

Prevalence—Number of continuing events, regardless of the time of their incidence, occurring simultaneously in any given population (for example, the prevalence of diabetes mellitus in Transylvania on December 1, 1967, was 6.1 percent).

position. Blood pressure was carefully monitored by manual sphygmomanometry throughout the test period.

Exercise Testing Results

The postexercise electrocardiogram was judged as abnormal if there was horizontal or downsloping ST segment depression of 1 mm or more which persisted for at least 0.08 seconds beyond the J point.[5-10] ST segment depressions of 0.5 and 0.75 mm were judged as borderline. ST segment changes of less than 0.5 mm were judged as normal. When a patient had resting ST segment depression, the postexercise ST segment depression was compared with that found in the resting state. In such cases there was only minor resting ST segment depression. Patients without positive EST results were further subdivided depending upon whether or not they achieved 90 percent of predicted maximum heart rate (PMHR) for age and sex. Two observers independently evaluated the EST results. Minor differences in interpretation were resolved by arbitration between these two observers.

Results

In 51 men with significant CAD (group A) there was either an unequivocally positive EST or negative EST after achieving 90 percent of PMHR (Table 1). Therefore, 18 men fell into a nondiagnostic category either because they failed to achieve 90 percent of PMHR or the postexercise ECG showed equivocal changes. The 41 men in whom there was a true positive EST and the 10 men in whom there was a false negative EST defined a sensitivity of 80.4 percent for this population (Tables 2 and 3).

Among the men in whom there were normal selective coronary arteriograms (group B), in four there was a positive EST finding and in 31 a negative EST finding while achieving 90 percent of PMHR (Table 1). In ten men EST results were nondiagnostic either because the patients failed to achieve 90 percent of PMHR or because the postexercise ECG showed equivocal changes. The four men with a false positive EST finding and the 31 men with a true negative EST finding defined a specificity of 88.6 percent for this population (Tables 2 and 3).

Discussion

The controversy surrounding the clinical usefulness of EST is due, in part, to a confusion of concepts and a lack of precise definitions (Table 2). Most commonly, EST is used as a noninvasive indicator of the presence or absence of CAD in patients complaining of chest pain suggestive of

TABLE 3.—*Review of Reports in the Literature Comparing Patients With Coronary Artery Disease Who Underwent Maximal EST With Patients Without Coronary Artery Disease**

	Martin[5] *A*	*Linhart*[6] *B*	*McHenry*[7] *C*	*Kelemen*[8] *D*	*Piessens*[9] *E*	*Ascoop*[10] *F*	*TOTAL*	*Vieweg et al*
True positive	39	57	70	26	20	26	238	41
False positive	4	4	4	1	5	3	21	4
True negative	21	42	76	23	22	49	233	31
False negative	10	14	16	22	18	18	98	10
Sensitivity	79.6%	80.3%	81.4%	54.2%	52.6%	59.1%	70.1%	80.4%
Specificity	84.0%	91.3%	95.5%	95.8%	81.5%	94.2%	91.7%	88.6%
Predictive value of + test	90.7%	93.4%	94.6%	96.3%	80.0%	89.7%	91.9%	91.1%
Predictive value of − test	67.7%	75.0%	86.2%	51.1%	55.0%	73.1%	70.4%	75.6%
Efficiency of test	81.1%	84.6%	88.0%	68.1%	65.7%	78.1%	79.8%	83.7%

EST = exercise stress testing

*Criteria similar to the present report were used to select patients from literature.

angina pectoris. However, EST has also been advocated as a screening test for CAD in apparently asymptomatic persons. The physician responsible for interpretation of the results and clinical significance of the postexercise ECG is presented with a vexing problem; that is, what is the relationship between electrocardiographic evidence of ischemia and coronary arterial anatomy. It is known that patients can have angina pectoris and positive findings on EST in the absence of CAD, as seen in valvular aortic stenosis and idiopathic hypertrophic subaortic stenosis. Moreover, many asymptomatic patients exercised several months after a documented myocardial infarction will have a negative EST. Therefore, EST results would seem to be a better index of myocardial ischemia rather than diseased coronary arterial anatomy, and evaluation of results of EST must be judged in this context. Since CAD is the most prevalent cause of myocardial ischemia in this country, it is to be expected that there is a secondary relationship between an abnormal postexercise ECG and CAD via the common pathway of myocardial ischemia.

The vast majority of our 69 men with CAD (group A) had two and three vessel disease and such cases were evenly distributed among those with positive, negative and equivocal EST findings. Not unexpectedly, the more extensive the CAD the easier it was to provoke positive EST findings. The mean heart rate achieved just before terminating the EST was 152 among those men with one vessel disease and a positive EST. For men with positive EST findings and two vessel or three vessel disease, the comparable heart rates were 139 and 129, respectively. In contrast, the men with a positive EST and normal coronary arteriograms achieved a mean heart rate of 186 just before terminating the EST (Table 1).

In the patients in group B (Table 1) coronary arteriograms were entirely normal without any luminal narrowing. None of these patients had hypertension, valvular or myocardial disease or were receiving medications known to influence myocardial repolarization. Their chest pain was judged to be at least suggestive of angina pectoris.

It has been repeatedly shown that maximal EST provides a higher yield of positive results than submaximal EST, just as the postexercise ECG per se is more useful in predicting CAD than the resting ECG. Accordingly, patients with a positive EST finding or a negative EST finding after achieving 90 percent of PMHR were included in our calculations (Table 3). Such patients were considered to have been maximally stressed and to have unequivocal postexercise ST segment depression. Using these criteria, the sensitivity (ability to recognize significant CAD when it was present) was 80.4 percent. If *all* negative EST results had been used in the calculations instead of only those of the men who had achieved 90 percent of PMHR, the sensitivity would have *decreased* to 65.1 percent. The specificity (ability to exclude any CAD when it was absent) was 88.6 percent. If all negative EST results had been used in the calculations instead of only those of men who had achieved 90 percent of PMHR, the specificity would have *increased* to 93.0 percent. The slight gain in specificity did not counterbalance the pronounced loss in sensitivity by including all negative EST results.

In group A, 18 of 69 men and in group B, 10 of 45 men had equivocal EST results either because they failed to achieve 90 percent of PMHR or their postexercise ST segment depression ranged between 0.5 and 0.75 mm (Table 1). Since neither a positive nor a negative EST result was found in these patients, one should not attempt to show changes in sensitivity or specificity by including such patients. It would be possible to define a "utility index" and include only those patients with a positive EST finding and CAD and those with a negative EST result after achieving 90 percent of PMHR and no CAD. If such an index were used it would be 59 percent in group A and 69 percent in group B.

The literature was reviewed in order to find patients who clinically resembled our own and who had undergone maximal EST and coronary arteriography in order to document the presence or absence of CAD (Table 3).[5-10] The findings in groups A and B were quite similar to those reported. The most striking finding was the paucity of false positive EST findings which provided a high degree of specificity (91.7 percent from the literature versus 88.6 percent for our group) and a high predictive value of a positive test (91.9 percent from the literature versus 91.1 percent for our group) (Table 3). Simply stated, this means that a positive EST result is more indicative of disease than a negative EST result is for the absence of disease in men complaining of chest pain.

It must be remembered that the population under discussion up to this point is a selected population because all were complaining of chest

TABLE 4.—*Accuracy of Exercise Stress Testing as a Function of Prevalence of Coronary Artery Disease*

	A*	B†
True positive	950	95
False positive	450	495
True negative	8,550	9,405
False negative	50	5
Sensitivity	95.0%	95.0%
Specificity	95.0%	95.0%
Predictive value of positive EST	67.9%	16.1%
Predictive value of negative EST	99.4%	99.9%
Efficiency of EST	95.0%	95.0%

EST = exercise stress testing

*A. Assume there is a population of 10,000 with a 10 percent prevalence of coronary artery disease in which the sensitivity and specificity of exercise stress testing are 95 percent.

†B. Assume there is a population of 10,000 with a 1 percent prevalence of coronary artery disease in which the sensitivity and specificity of EST are 95 percent.

pain. Not all patients described classical angina pectoris; however, patients complaining of chest pain provide a population in which one is more likely to find CAD than in a population free of chest pain. Indeed, when a patient complains of chest pain typical of angina pectoris, the correlation with arteriographic CAD approaches 90 percent.[11] As one moves from a population with a high prevalence of CAD to a population with a low prevalence of CAD, the usefulness of EST will change considerably. As noted in Table 4, a change in prevalence of CAD from 10 percent to 1 percent decreases the predictive value of a positive test from 67.9 to 16.1 percent although the sensitivity and specificity of the test in this example are 95 percent. This statistical fact raises serious problems for EST as a screening procedure in asymptomatic persons, particularly in a population with a low prevalence of CAD.

Two recent articles have been widely quoted as depreciating the usefulness of EST in predicting CAD.[1,2] Both articles employed a risk factor other than chest pain to define their populations. In the paper by Borer and co-workers,[1] type II hyperlipoproteinemia was the common denominator and in the paper by Froelicher and associates,[2] asymptomatic patients with resting electrocardiographic repolarization abnormalities were selected for study. Since EST reflects ischemia, and since both of these populations were selected by a factor that correlates less with ischemia than does chest pain, it is not surprising that the results of these two studies differ from our own. The reader must be wary of attempts to predict anatomy rather than ischemia with EST.

We conclude that in an American male population referred for evaluation of chest pain and free from hypertension, valvular or myocardial disease and not receiving medications known to influence electrocardiographic repolarization, EST to an end point of 1 mm ST segment depression or 90 percent of PMHR is a highly useful predictor of associated CAD. That is, chest pain due to myocardial ischemia (angina pectoris) can be distinguished from noncardiac chest pain using maximal EST. It must be recognized that a significant number of patients will fall into a nondiagnostic category either because symptoms develop that preclude their reaching 90 percent of PMHR or because the postexercise-electrocardiographic changes fall into a borderline category between 0.5 and 0.75 mm ST segment depression. It must also be recognized that when a male population is selected on some basis other than for evaluation of chest pain, the maximal EST is much less useful as a predictor of associated CAD.

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The Biology of the Rheumatoid Synovial Cell

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Over the past 15 years, many of the elaborate research techniques of cell biology and biochemistry have been applied toward discovering the cause of rheumatoid arthritis. Consequently, it is valuable to review the morphological, physiological and biochemical alterations that have been observed in rheumatoid synovial cells. All of the changes observed suggest that a viral agent may form the basis for these alterations. However, studies to date have failed to isolate or identify the putative causative virus and the search continues.

In the first two decades of the 20th century, rheumatoid arthritis was known as "chronic infectious arthritis." Over the next 30 years, this terminology was abandoned because of the overwhelming failure to reproducibly culture a microbe from rheumatoid joints. Attention was then directed to an alternate cause of rheumatoid arthritis when it was discovered that serum rheumatoid factors from patients with rheumatoid arthritis were autoantibodies to immunoglobulins.[1] As a consequence of this discovery, it was hypothesized that rheumatoid arthritis was an autoimmune disease. After many years of research to define the role of autoimmunity in rheumatoid arthritis, it has become clear that both the humoral and cellular immune systems are intimately involved in the inflammatory reaction that characterizes rheumatoid synovitis.[2] However, it has become equally clear that some abnormality independent of the immune system is probably involved in initiating the immunopathological events.

In search of this abnormality, a number of investigators have directed their attention to the rheumatoid synovial membrane and its component cellular elements. These studies have not only detected a number of physiological and biochemical alterations in rheumatoid synovial cells but have also shown that these alterations persist in synovial cells grown *in vitro* under conditions that preclude continuing immunological and inflammatory events. Because these changes in rheumatoid synovial cells bear some resemblance to the cellular disturbances that result from viral infections, the prevailing current speculation on the cause of rheumatoid arthritis is a recommitment to the notion that an infectious agent is involved.[3-5]

In this paper we will review some of the morphological, physiological and biochemical abnormalities that occur in rheumatoid synovial cells and indicate how these changes support the concept that a viral agent may be the basis of rheumatoid synovitis. We will also summarize some of the recent attempts to isolate and identify the presumed causative virus.

Morphology and Function of Normal Synovial Membrane

The diarthrodial joints in humans are, in effect, body cavities and it is these cavities that suffer the ravages of rheumatoid synovitis. The joint cavity wall consists of two layers—the capsule and the synovial membrane (Figure 1).[6] The

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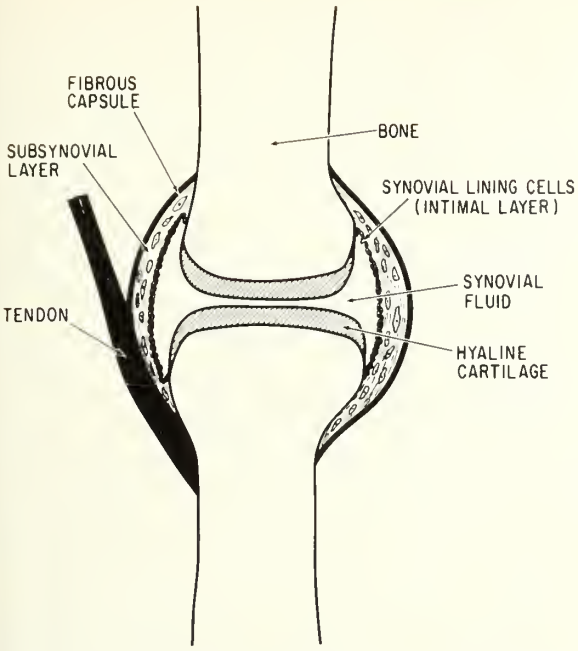

Figure 1.—Diagramatic representation of the morphology of a normal diarthrodial joint. See text for details.

outer layer, the capsule, is composed of dense collagenous fibrous tissue and frequently merges with periarticular tendons. Inward, toward the joint cavity, the fibrous capsular tissue is replaced by a more delicate arrangement of collagenous tissue which contains fibroblasts, macrophages and capillaries; this is the subsynovial layer of the synovial membrane. Covering the subsynovial layer and immediately adjacent to the joint cavity is the intimal layer; this portion of the synovial membrane consists of synovial lining cells which encircle the entire joint cavity with a continuous layer one to three cells in thickness.[7] (It should be noted that the term synovial lining cells, also termed synovial intimal cells or synoviocytes, is arbitrary nomenclature because these cells are probably a heterogeneous mixture perhaps closely related or identical to cells found in the subsynovial layer.) Most of the investigational work on the cell biology of the synovial membrane has focused on synovial lining cells and, as a consequence, this review will concentrate on these cells.

The synovial lining cells are not arranged in a tightly packed, uninterrupted layer. On the contrary, the lining cells are loosely arranged in an intercellular fibrillar material composed mainly of collagen and reticular fibers with elastic fibers found rarely.[7] Unlike other body cavity lining cells, there are no desmosomes joining the synovial cells and there is no basement membrane between the intimal and subsynovial layers.[8,9] Indeed, there are open channels of communication between the joint cavity and the subsynovial layer which freely permit passage of colloidal gold particles.[9]

Using electron microscopy and cytochemical techniques, Barland and colleagues have defined three morphologically and perhaps functionally distinct cell types in the synovial lining layer.[8] The type A cells account for about two thirds of the lining cells and are characterized by an abundance of filopodia, large intracellular vacuoles and micropinocytotic vesicles, intracellular fibrils and a prominent Golgi apparatus; because of morphological similarities to macrophages, some investigators have referred to this cell type as M cells.[10,11] Morphologically, the type A cell appears well suited for phagocytic and catabolic functions and evidence for this has been provided by experiments which have shown that intraarticularly injected colloids are ingested by type A cells.[12-14] Whether this function is important in maintaining normal joint homeostasis is uncertain, but it may be a mechanism by which large molecular weight proteins are removed from joint fluid under pathological conditions.[15]

Another third of the synovial lining cells are termed type B and are characterized by abundant endoplasmic reticulum, with vacuoles and filopodia being much less prominent than in type A cells.[8] Because of a morphological similarity to fibroblasts, some authors prefer to call these F cells.[10-11] Type B cells have an abundant macromolecular synthetic machinery in the form of endoplasmic reticulum and are consequently thought to be the cells of origin of many of the synovial fluid macromolecules, particularly hyaluronate-protein.[16]

A small number of normal synovial lining cells have morphological features that overlap both A and B cell types; these have been referred to as type C or intermediate cells, but their precise precursor relationship, if any, to type A and B cells is unknown.[8-11]

Beneath the synovial lining cells, in the immediately adjacent subsynovial layer, is a capillary network that is within 3 to 4 microns from the synovial space. These capillaries are characterized by attenuated endothelial cells which are separated by numerous fenestrations bridged by a thin membrane.[17,18] These anatomical features are similar to the vasculature of the renal

glomerulus and the choroid plexus and are eminently suited for the prime function of the synovial membrane—this is, the rapid exchange of water and low molecular weight metabolites between the vascular space and the joint fluid. The mechanism by which this specialized microvasculature selectively excludes high molecular weight plasma proteins from the joint space is not understood. Moreover, it is uncertain whether factors other than permeability properties of the vasculature *per se* regulate solute and water movement into the joint space. In the absence of a basement membrane or of desmosomes, the exact role the synovial lining layer may play as a barrier between the vascular bed and the joint cavity is also uncertain. There is some suggestive evidence that intercellular hyaluronate-protein in this layer may provide a chemical barrier that selectively excludes some macromolecules.[19]

Joint fluid is the combined end product of a plasma filtrate from the subsynovial capillaries and macromolecules synthesized by the synovial lining cells; the properties of normal joint fluid are summarized in Table 1. Synovial fluid is the major source of nutrients for the avascular cartilage and has specific physiochemical properties that facilitate motion of articulating surfaces. The main contributor to the lubricant properties of synovial fluid is presumed to be a complex of high molecular weight hyaluronate and protein. Synovial fluid hyaluronate is an acidic glycosaminoglycan with repeating units of N-acetyl-D-glucosamine and D-glucuronic acid with a molecular weight of 5 to 10 million daltons;[20] it is synthesized by synovial lining cells, presumably type B cells.[16] Much less is known of the protein component, even though recent studies suggest that it is the major determinant of the lubricant property of the hyaluronate-protein complex.[21] For example, the site of synthesis and the number of different proteins involved in the complex is uncertain, and the nature of the linkage between protein and hyaluronate is unknown. In fact, it is possible that the complex of hyaluronate and protein is an artifact of chemical isolation procedures.

Morphology and Function of Rheumatoid Synovial Membrane

With the preceding background information on normal synovial membrane morphology and function, we now turn attention to the abnormal features found in the synovium of rheumatoid arthritis. By light microscopy, several architectural alterations are seen that are very characteristic, but not diagnostic, of rheumatoid synovitis (Figure 2).

The overall structure of the subsynovial layer remains basically intact but the normal cellular elements are present in notably increased numbers, especially increased numbers of lymphocytes and plasma cells which are scattered throughout an increased amount of a fibrillar ground substance.[9] The subsynovial microvasculature appears unaltered without significant endothelial hyperplasia, degeneration or vascular occlusion.[9,22] However, when viewed under the electron microscope, the subsynovial vasculature showed some intriguing findings. Ghadially and Roy noted fine filamentous fibers in capillary

TABLE 1.—*Characteristics of Synovial Fluid Components From Normal and Rheumatoid Joints**

	Normal synovial fluid	*Rheumatoid synovial fluid*
Cells	<50 per cu mm—mononuclears	>10,000—mostly neutrophils
Glucose	Serum levels	<Serum levels
Electrolytes and low molecular weight metabolites	Serum levels	Serum levels
Plasma proteins	<2.5 gm per 100 ml	>4 gm per 100 ml
albumin	67%	37%
globulins	33%	63%
Clotting factors	Absent	Present
Complement components	Absent	Reduced in comparison with other plasma proteins
Hyaluronate	0.3 gm per 100 ml—high molecular weight	0.1 gm per 100 ml—low molecular weight
Lysosomal enzymes	Low levels	Increased
Collagenase	Absent	Present

*Modified from Hamerman et al.[19]

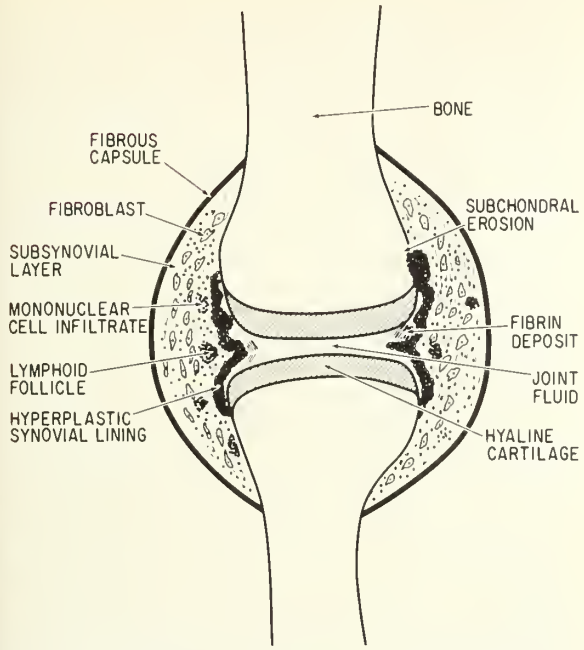

Figure 2.—Diagramatic representation of the morphology of a rheumatoid joint. See text for details.

endothelial cells of rheumatoid synovium; however, these fibers were also seen, but to a lesser extent, in normal synovium and their composition remains unknown.[22] Other investigators have noted intracellular rod-shaped bodies in subsynovial endothelial cells of rheumatoid tissue; although dimensions vary, the bodies have been described as being 0.4 to 1.6 microns in diameter and contain tubular elements 80 to 150 angstroms in diameter.[23-25] These intracellular inclusions were also occasionally seen in mononuclear cells but never in synovial lining cells. The presence or quantity of these intracellular inclusions did not correlate with the duration or severity of rheumatoid arthritis.[24] Since these inclusion bodies have structural similarities to viral inclusions, their presence has been used to support the concept of a viral cause for rheumatoid synovitis. Unfortunately, the simplicity of this argument has been complicated by observations that subsynovial endothelial cells in normal human and animal synovial membranes, as well as patients with osteoarthritis, contain similar intracellular inclusions.[18,22] At present, the precise nature and significance of these intracellular inclusions are uncertain.

In the early stages of rheumatoid synovitis, hyperplasia of the synovial lining cells is a characteristic feature with the lining cells being more closely packed and extending two to six cells deep.[26] This hyperplasia progresses during the course of rheumatoid synovitis.[9,10,22] Areas of fibrin-like material can be found on the synovial cell surface and in the intercellular spaces. Electron microscopy shows this material to have the axial periodicity of fibrin and it has been suggested that this extravascular fibrin deposition is secondary to some degree of subsynovial vascular damage.[27] The synovial lining is remarkably free of the mononuclear cell infiltrate seen in the subsynovial layers and, despite the sometimes extensive hyperplasia, the intimal lining remains structurally intact.[9]

Since the light microscopic features of the rheumatoid synovial lining layer are shared by other forms of inflammatory arthritis, many electron microscopic studies of this layer have been carried out with the hope of defining abnormalities specific for rheumatoid arthritis. Type A synovial lining cells show significant morphological changes characterized by fewer filopodia, a less well-developed Golgi apparatus, and swelling and distortion of mitochondria. In addition, rheumatoid type A cells contain numerous membrane-limited granular dense bodies that are rarely seen in normal synovial lining cells.[22,27,28] Barland and colleagues suggest that these dense bodies represent phagolysosomes containing materials ingested from inflammatory joint fluid;[28] on the other hand, Wylie suggests that these bodies are autophagocytic vacuoles resulting from the cell's attempt to digest focal areas of damaged cytoplasm.[27] Whatever their cause, similar types of granular dense bodies are seen in other types of inflammatory synovitis and may represent a nonspecific cellular reaction to a variety of noxious stimuli.[22] Rheumatoid type A synoviocytes also contain a large number of ferritin granules in phagolysosomes. It is presumed that this ferritin is the product of the phagocytosis and breakdown of hemoglobin which originates from intraarticular microhemorrhages that occur during an active inflammatory synovitis.[29,30] Ferritin may perpetuate rheumatoid inflammation by rendering lysosomes more susceptible to rupture with the subsequent release of lysosomal enzymes.[29] Compared with type A cells, type B cell ultrastructural changes are considerably more subtle, with hyperplasia of the endoplasmic reticulum and distortion of mitochondria being the major changes.[22] However, there is an increase in the relative proportion of type B cells.[22,27]

By immunofluorescent microscopy, rheumatoid type A and C synovial lining cells are shown to contain immunoglobulins and complement. In both seropositive and seronegative patients, these cells show a diffuse granular deposition of IgG and C3. In addition, lining cells from seropositive patients show large discrete granular deposits of IgG, IgM and C3.[31,32] Similar immunofluorescent staining patterns are rarely seen in the synovium from patients with other varieties of inflammatory synovitis.[31] The immune deposits in rheumatoid synovial lining cells are presumed to result from *in vivo* phagocytosis of immune complexes present in joint fluid. This presumption is supported by the observation that the immunofluorescent patterns observed in rheumatoid synovium are very similar to the patterns seen in experimental antigen-induced arthritis in animals which is immune complex mediated.[33] There is no positive correlation between the degree of immunoglobulin deposition and the degree of synovitis, however, and whether these deposits are antigen-antibody complexes remains uncertain.[31]

Abnormalities in the structure of rheumatoid synovium are reflected by major changes in the composition of joint fluid (Table 1). Because of disruption of the normal permeability barriers in the subsynovial vasculature, rheumatoid joint fluid contains an increased quantity of high molecular weight plasma proteins which are present in much lower or undetectable amounts in normal joint fluid.[34] In addition, some of the increase in IgG and IgM in rheumatoid joint fluid results from the local synthesis of these immunoglobulins by lymphocytes and plasma cells in the rheumatoid synovial membrane.[35,36] The hyaluronate-protein complex in rheumatoid joint fluid is present in a lower concentration than normal. This does not represent diminished synthesis; if one corrects for the much larger volume of fluid in a rheumatoid joint, the total amount of hyaluronate-protein is actually increased.[20] The hyaluronate component of the complex has a lower molecular weight of 2 to 4 million daltons rather than the normal 5 to 10 million.[20,37] The lower molecular weight of hyaluronate may result from the action of lysosomal hyaluronidase released by intraarticular polymorphonuclear leukocytes, although this enzyme has minimal activity above pH 4.5.[38] It is more likely that superoxide radicals cause the degradation of hyaluronate; superoxide radicals are produced by phagocytizing polymorphonuclear leukocytes which are abundant in rheumatoid joint fluid.[39] Less is known about the protein component of the hyaluronate-protein complex in rheumatoid synovial fluid, although there have been some suggestions that this component is increased.[37] Further work at identifying the increased protein moiety has characterized it as a serum protein, inter-alpha trypsin inhibitor, which is probably derived from serum and becomes tightly bound to hyaluronate as it passes from serum into the diseased joint.[40] For many years it was assumed that the altered physiochemical properties of rheumatoid hyaluronate-protein would significantly alter the lubricant properties of rheumatoid synovial fluid; however, direct measurements have shown that synovial fluid from rheumatoid joints lubricates synovial membranes in a manner similar to normal fluid.[21]

As alluded to above, rheumatoid synovial fluid contains an abundance of polymorphonuclear leukocytes which are active in the phagocytosis of intraarticular immune complexes.[41] These white cells release a number of catabolic lysosomal enzymes, such as acid phosphatase, β-glucuronidase, β-acetyl glucosaminidase and cathepsins, into the joint fluid.[42,43] Moreover, these same enzymes are present in increased amounts in rheumatoid synovial membrane where their source is thought to be the type A lining cells.[43] It is perhaps this latter source of catabolic enzymes that is important in the joint destruction of rheumatoid arthritis, since there is a positive correlation between the enzyme concentrations in homogenates of rheumatoid synovium and the degree of joint destruction, but not between synovial fluid enzyme levels or white cell content.[43]

Cell Biology of Rheumatoid Arthritis

Although a disease similar to it occasionally occurs spontaneously in animals,[44,45] rheumatoid arthritis generally is considered a disease unique to man. Furthermore, an experimentally induced animal model of rheumatoid arthritis is not available. As a consequence, dynamic studies of the physiology and biochemistry of the rheumatoid synovial membrane require *in vitro* techniques.

Early attempts at studying the metabolism and biochemistry of rheumatoid synovial tissue *in vitro* utilized organ culture techniques.[46,47] Interpretation of these studies was complicated by the fact that rheumatoid tissues are infiltrated with lymphocytes, plasma cells and other cells whose metabolic activities contribute to that of the whole

TABLE 2.—*Characteristic Alterations in Isolated Rheumatoid Synovial Cells*

- Increased generation time
- Decreased *in vitro* life span
- Increased glucose utilization
- Increased lactate production
- Increased activity of diphosphopyridine nucleotide (DPNH)-diaphorase
- Increased synthesis of a low viscosity hyaluronate
- Synthesis of a soluble collagen of subnormal molecular weight
- Decreased production of a cartilage-like protein polysaccharide
- Increased content of lysosomal enzymes
- Relative unresponsiveness to glucocorticosteroids
- Increased content of endogenous connective tissue activating peptide (CTAP)

tissue.[48] Consequently, a significant technical advance toward the *in vitro* study of rheumatoid synovial tissue was made when Castor, based on the earlier work of Vaubel,[49] developed a reliable cell culture method for growing and propagating human synovial lining cells.[50] Since this development, considerable research has been done comparing normal and rheumatoid synovial cells in culture, and numerous differences have been defined (Table 2).

Cultures of synovial cells are generally obtained as outgrowths from explants of synovial tissue obtained at surgical operation; before placing the explant in a culture vessel, an attempt is made to dissect away the subsynovial tissue and thereby ensure that the cells that eventually grow from the explant are from the synovial lining layer.[50] However, since this layer is probably a heterogeneous mixture of cells, the resultant tissue culture population is probably a mixture of cell types. Synovial cells can also be isolated by centrifugation of joint fluid[51] and a method has been described for obtaining synovial cells from autopsy specimens by the intraarticular instillation of a trypsin solution.[52]

Utilizing these types of isolation techniques, monolayers of "fibroblastic" cells that resemble the type C cell seen in intact synovial membranes can be reproducibly obtained.[53] Cultured rheumatoid synovial cells have a tendency to form multinucleated giant cells with bizarre-shaped nuclei;[51,53-56] since the formation of multinucleated cells is a cytopathic effect of a number of viruses, some have suggested that this is evidence that rheumatoid synovial cells are infected with a virus.[55] However, multinucleated giant cells have also been observed in synovial cultures from patients with osteoarthritis[51] and other inflammatory arthropathies.[57] Moreover, electron microscopic studies of cultured rheumatoid synovial cells have not shown morphological evidence of a viral infection.[57,58]

In culture, rheumatoid synovial cells display characteristic alterations in their growth patterns when compared with normal synovial cells. Numerous investigators have observed that isolated rheumatoid synovial cells have a generation time (this is the time required for doubling) which is twice as long as for normal cells.[51,54,59] In addition, rheumatoid synovial cells have a diminished *in vitro* life span when compared with nonrheumatoid cells.[54,59] These *in vitro* properties of rheumatoid synovial cells are somewhat contrary to what one would expect since intact rheumatoid synovium is characterized by pronounced overgrowth and hyperplasia of the synovial lining layer. Indeed, *in vitro* studies of intact rheumatoid synovial slices show higher proliferation rates for rheumatoid synovial lining cells than do lining cells from osteoarthritic synovium.[60] At present, it is not possible to explain the diminished rate of cell division of isolated rheumatoid synovial cells grown *in vitro*.

A variety of metabolic and biochemical abnormalities have been noted in cultured rheumatoid synovial cells. What is most significant about these abnormalities is that they are similar to changes noted in intact rheumatoid synovial membrane and they correlate with alterations measurable in rheumatoid joint fluid. In addition, these abnormalities are persistent and characteristic of rheumatoid synovial cells for their entire *in vitro* life span.[59] Isolated rheumatoid synovial cells, similar to intact rheumatoid synovial membranes,[47,48] utilize increased quantities of glucose and produce increased quantities of lactate, suggesting that glycolysis is a major energy-producing pathway in these cells.[61] Because of an apparant increase in the activity of the glycolytic cycle, some glycolytic pathway enzymes have been examined. At least one enzyme, diphosphopyridine nucleotide (DPNH)-diaphorase, is increased in intact rheumatoid synovium and this increased enzyme content persists for many generations in cultured rheumatoid synovial cells.[53]

Rheumatoid synovial fluid contains an abnormal hyaluronate characterized by a lower than normal molecular weight and a lower viscosity.[20,37,62] Rheumatoid synovial cells in culture

synthesize hyaluronate and, interestingly, this is also of lower viscosity when compared with the hyaluronate produced by synovial cells from normal or osteoarthritic joints.[61,63] Despite the fact that isolated rheumatoid synovial cells synthesize an abnormal hyaluronate, the total production of this macromolecule is increased.[61]

There is evidence that rheumatoid synovial membrane contains a chemically modified form of collagen[64] and that many types of inflamed synovial tissue, including rheumatoid, have an increased proportion of type III collagen.[65] Isolated rheumatoid synovial cells may reflect this abnormality, since the soluble collagen synthesized by these cells *in vitro* is of subnormal molecular weight.[63] The noncollagenous matrix of cartilage consists of a variety of physically and chemically distinct proteinpolysaccharide complexes. Using immunochemical methods, it has been shown that synovial lining cells synthesize at least one of these proteinpolysaccharide complexes and that rheumatoid synovial lining cells contain less of this material than normal cells.[66] Rheumatoid synovial cells grown *in vitro* reflect this same abnormality since they also produce less of this proteinpolysaccharide complex than normal cells.[66]

As described earlier, intact rheumatoid synovial membranes have a notably increased content of lysosomal hydrolytic enzymes.[42,43] Using histochemical techniques, it has been shown that these same lysosomal enzymes are elevated in cultured rheumatoid synovial cells and this persists through many generations *in vitro*.[67]

Glucocorticoid hormones induce a variety of changes in cultured human synovial cells including: accelerated cell proliferation, reduced cell volume, reduced rate of hyaluronate synthesis, decreased viscosity of the hyaluronate synthesized and secreted, and decreased deposition of collagen.[68-70] Cultured rheumatoid cells, in contrast to normal synovial cells or cells from other types of inflammatory arthritis, are relatively resistant to these effects of glucocorticoids.[51,63]

Over the past five years, evidence has accumulated suggesting that many of the above-described biochemical and metabolic abnormalities in rheumatoid synovial cells are explicable on the basis of a single biochemical alteration. Castor noted that a low molecular weight peptide (termed connective tissue activating peptide or CTAP), which can be isolated from a variety of cells and tissues (including normal and rheumatoid synovium, polymorphonuclear leukocytes, lymphocytes, spleen cells, muscle, kidney and some tissue culture cell lines), induces normal synovial cells to increase glucose utilization and lactic acid production, increase synthesis of a low viscosity hyaluronate, decrease synthesis of soluble and fibrous collagen, and become relatively unresponsive to glucocorticosteroids[61,71,72] (Table 3). As described previously, all these effects are similar to those seen with cultured rheumatoid synovial cells in the absence of this peptide. Interestingly, rheumatoid synovial cells are unresponsive to exogenous CTAP and the likely cause of this unresponsiveness is that rheumatoid cells already contain a four-to-five-fold increase of endogenous CTAP.[61] Furthermore, many of the antirheumatic drugs, including aspirin, indomethacin, phenylbutazone and cortisol, block the effect of CTAP on normal synovial cells;[73] this effect may be the basis for some of the therapeutic efficacy of these drugs. Prostaglandins have been implicated in the inflammatory process and are capable of inducing many of the same effects on synovial cells as CTAP. Indeed, prostaglandins have been shown to potentiate the effect of CTAP itself.[74] Despite the fact that CTAP, perhaps in conjunction with prostaglandins, provides a unified molecular mechanism to account for many of the metabolic and biochemical abnormalities of rheumatoid cells, the key issue is what event initiates and perpetuates the elevated levels of endogenous CTAP in rheumatoid synovial cells—even after many generations in culture.

TABLE 3.—*Effects of CTAP on Cultured Normal Synovial Cells*

Increases glucose utilization
Increases lactate production
Increases synthesis of a low viscosity hyaluronate
Decreases synthesis of soluble and fibrous collagen
Induces unresponsiveness to glucocorticosteroids

CTAP = connective tissue activating peptide

In addition to providing evidence for a primary alteration in some of the biochemical and metabolic processes of rheumatoid synovial cells, tissue culture techniques have aided in understanding some of the mechanisms of the cartilage and bone destruction that characterizes rheumatoid synovitis. Early *in vitro* work showed that monolayers of rheumatoid synovial cells digest cartilage fragments because of the release of enzymes from synovial cells and not as a result of cellular invasion of the cartilage fragments.[75] Cartilage was not digested by normal synovial

cells or cells from a patient with Reiter syndrome.[75] Some of the dissolution of cartilage matrix is probably mediated in part by lysosomal proteases.[76] These proteases probably derive from synovial type A cells which, during the process of phagocytosis, release lysosomal proteases.[77]

However, in that 90 percent of the protein matrix of cartilage is collagen, which is relatively resistant to the usual lysosomal proteases, numerous investigators have sought an enzyme that would specifically degrade native collagen. In 1968 a collagenase released by explants of cultured rheumatoid synovial tissue was described.[78,79] At 20° to 27°C and neutral pH, this enzyme degrades native collagen into fragments of ¾ and ¼ length; at 37°C, these fragments are broken down further into low molecular weight peptides.[78,79] A positive correlation was noted between the amount of synovial membrane collagenase and the degree of disease activity as measured by the amount of synovial proliferation and inflammation observed histologically.[79] Collagenase is not unique to rheumatoid synovium since it can also be found in synovium from other inflammatory arthropathies and occasionally in osteoarthritis.[80]

Because collagenase is probably the most significant enzyme involved in the destructive changes of rheumatoid arthritis, much work has been devoted to understanding its enzymology in the hopes of eventually developing therapeutic modalities that could inhibit the destructive actions of the enzyme. Purified rheumatoid synovial collagenase is an enzyme with a lower molecular weight and a more basic charge than a similar extensively studied enzyme from skin.[81] Degradation of cartilage collagen by the purified enzyme is temperature-dependent to a pronounced degree, with the rate increasing fourfold from 33°C (the temperature of normal joints) to 36°C (the temperature of a rheumatoid joint).[82] Since rheumatoid joint temperature is elevated secondary to inflammation, these findings suggest that anti-inflammatory agents may serve to decrease joint destruction in rheumatoid synovitis. Since cleavage of native collagen by purified collagenase is into a ¾-length fragment and a ¼-length fragment, further degradation to lower molecular weight peptides is probably a function of an endopeptidase which is also present in rheumatoid synovium.[83]

The precise cellular origin of the collagenase present in rheumatoid synovium remains controversial. Rabbit synovial lining cells grown *in vitro* produce a collagenase.[84] In addition, polymorphonuclear leukocytes and macrophages also release collagenases.[85,86] Because most studies of collagenase biochemistry and physiology have utilized explants of tissue, the relative contribution of each cell type to the total collagenase production is unknown. Recent cell culture experiments with human material have failed to resolve this controversy, although it is suggested that type A synovial cells are certainly a major source of collagenase.[87]

A number of *in vitro* studies suggest a variety of control mechanisms of collagenase activity *in vivo*. The important role of intraarticular temperature has already been alluded to above.[82] Normal serum and most normal synovial fluids contain a factor that inhibits collagenase activity.[88,89] This factor is a protein of the alpha$_2$-macroglobulin fraction with a molecular weight of 40,000; this low molecular weight probably permits access of the inhibitor to normal body fluids.[89] Interestingly, rheumatoid synovial fluid may contain less inhibitor than normal joint fluid or else rheumatoid synovium produces a collagenase which is insensitive to the inhibitor.[90]

Other studies of mechanisms that control collagenase activity have shown that human polymorphonuclear leukocytes release an inactive procollagenase during phagocytic ingestion of immune complexes;[91] in the presence of rheumatoid but not normal synovial fluid, this procollagenase is activated.[91] Phagocytic macrophages and synovial lining cells also release collagenases upon ingestion of aggregated materials.[77,86] Macrophages and synovial cells also secrete collagenases upon stimulation by lymphokines released from mitogen-stimulated or antigen-stimulated lymphocytes and, since rheumatoid synovium is heavily infiltrated with lymphocytes, this mechanism of collagenase release may apply in rheumatoid synovitis.[92,93]

Tissue culture methods have been applied to studies of potentially beneficial pharmacological agents for rheumatoid arthritis. Clearly it would be of value to have an *in vitro* means of assessing the potential effect of a variety of therapeutic modalities on the biochemical and metabolic abnormalities of rheumatoid synovitis. That this approach is feasible has been shown by the observation that glucocorticosteroids inhibit collagenase release by cultured rheumatoid synovium.[94]

The Search for an Etiologic Agent

The possibility that an infectious agent might cause rheumatoid arthritis has provoked many investigations directed toward identifying and isolating the organism(s). Early in this century, numerous bacterial species were implicated as causative agents, but repeated bacteriological, serological and epidemiological studies have failed to prove this point. Within the past 20 years, sporadic reports have implicated a variety of mycoplasma species as causative of rheumatoid arthritis. However, recent studies, using the most sophisticated bacteriologic and biochemical techniques available, have totally failed to discover any evidence of mycoplasmas in synovial tissue from patients with rheumatoid arthritis.[95,96] As a consequence, it is now generally accepted that mycoplasmas are not etiologically linked to human rheumatoid arthritis.

A viral infection is currently considered the most likely cause of rheumatoid arthritis.[3-5] Observations in support of this hypothesis include the viral-like inclusion bodies noted by some investigators in rheumatoid synovial tissue.[22-25] However, as discussed previously, there is no definitive proof that these inclusions are viral in nature, nor are they specific for rheumatoid arthritis.[18,22] Perhaps the most convincing support of a viral basis for rheumatoid synovitis are the observations that many of the biochemical and physiological alterations in rheumatoid synovial cells are similar to alterations induced in normal fibroblasts by viral infections. For example, increased glucose utilization and lactate production, increased hyaluronate synthesis, and increased release of lysosomal enzymes have all been observed after viral infection of fibroblasts *in vitro*.[97-101]

Despite the circumstantial evidence, there is to date no direct proof that rheumatoid arthritis is caused by a virus. Using the conventionl virological technique of observation for a cytopathic effect after addition of homogenates of rheumatoid synovial tissue to a variety of tissue culture cell lines, numerous investigators have failed to detect any evidence of a virus in rheumatoid tissue.[102-105] Warren and colleagues have noted that a bacteria-free and mycoplasma-free extract of rheumatoid synovial tissue induced congenital joint and skeletal lesions in mice and chickens and suggested that this resulted from a virus in the extract.[106-109] However, repetition of these experiments by others showed that both rheumatoid and nonrheumatoid synovial tissue extracts induced similar lesions and they occurred only in a small percentage of the mice or chickens.[95] Utilizing techniques that have provided definitive evidence for a latent virus in some instances of virus-induced neoplasia, a latent virus has not been detected in cultured rheumatoid synovial cells.[96,110-112] Because of the association of a ribonucleic acid (RNA)-dependent deoxyribonucleic acid (DNA) polymerase ("reverse transcriptase") with infection by latent oncogenic viruses, some investigators have searched for this enzyme activity in rheumatoid synovial cells but none was detected.[111,113,114]

Since conventional and even elaborate virological techniques have failed to provide evidence for a virus or viral genes in rheumatoid synovial cells, a number of investigators have tried some indirect methods to provide evidence for a viral infection. Grayzel[115] and Smith and Hamerman[53,59] have reasoned that, if rheumatoid synovial cells are infected by a latent virus, then these cells may be resistant to infection by another virus. Based on this rationale, these workers have shown that rheumatoid synovial cells are resistant to infection by rubella[115] and Newcastle disease viruses.[53,59] Moreover, the resistance to rubella virus can be transferred to rabbit synovial cells by injecting human rheumatoid synovial cells into rabbit joint[116] or by fusing human rheumatoid synovial cells with rabbit cells.[117] However, at least six other laboratories have attempted to reproduce the experiments showing resistance of rheumatoid synovial cells to rubella or Newcastle disease infections and have failed.[104,110,118-122] These divergent results can be explained by the observation that rheumatoid synovial cells are occasionally resistant to viral infection because of an envelope of hyaluronate-protein around rheumatoid synovial cells; if this envelope is digested away, rheumatoid synovial cells have the same sensitivity to viral infection as normal cells.[123,124]

It should be clear from the above that, despite the application of the most sophisticated of scientific techniques by many laboratories, the etiologic agent of rheumatoid arthritis remains elusive. Perhaps infection in the usual sense is not involved in rheumatoid arthritis, but may only occur as a transient triggering event. The recent experiments by Buckingham make this an attractive possibility. He has shown that extracts from

Gram-negative bacteria induce normal synovial cells to increase hyaluronate production, to become insensitive to connective tissue activating peptide, and to increase endogenous concentrations of connective tissue activating peptide.[125,126] All these changes are similar to those seen in rheumatoid synovial cells. Of prime importance is that these changes persist in normal synovial cells for more than 30 days after exposure.[126] By this type of mechanism, an infectious agent may trigger rheumatoid arthritis but not persist in the joint to be isolated at a later date.

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Specialty Conference

Participants

JACK C. SIPE, MD
JAY H. ROSENBERG, MD

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Granulomatous Giant Cell Angiitis of the Central Nervous System

JACK C. SIPE, MD:* An 81-year-old man was admitted to hospital because of deteriorating mental function. He was in good health except for mild cardiac difficulties for which he took quinidine and digoxin. Three years before admission a squamous cell carcinoma of the right part of the palate and tonsillar fossa was diagnosed and he was treated with 7,000 rads of local irriadiation followed by radical neck surgical procedures. On pathologic examination of the retromandibular lymph nodes, no evidence of metastatic carcinoma was found. For two years preceding admission the patient was noted to be occasionally forgetful and at times mildly confused. Five weeks before admission herpes zoster developed on the left side of the forehead and the patient was treated for two weeks with tapering doses of corticosteroids. Subsequently, severe lancinating facial pain occurred several times a day. Four weeks before admission, the patient noted a "top-heavy" sensation and required a cane for walking. He began falling without loss of consciousness or seizure activity and was admitted to hospital after suddenly falling out of a chair forward and to the right.

Findings on neurological examination included a relatively normal mental state, nystagmus on horizontal and vertical gaze, a mild pronation drift of the right arm and striking ataxia of the right arm and leg. The patient was unable to stand without assistance and consistently fell to the right. The deep tendon reflexes were normal in the arms, increased at the right knee compared with the left and absent at the ankles. The right plantar response was extensor, the left flexor. The sensory examination disclosed no consistent abnormalities. A diagnosis of brainstem lacunar infarction was made. Carbamazepine (Tegretol®) was given for postherpetic neuralgia with moderate success. A brain scan was normal.

Within two days of admission there was loss of the right arm drift and less right-sided ataxia. Truncal ataxia persisted, however, with continued falling to the right. A decline in mental facility was noted while the patient was in hospital; by the 17th hospital day the patient was oriented only to person and place and could follow only one part commands. On lumbar puncture slightly xanthochromic spinal fluid was found with an opening pressure of 150 mm of cerebrospinal fluid (CSF). There were 42 cells, predominantly lymphocytes, a protein value of 90 mg per 100 ml, and a glucose level of 55 mg per 100 ml. A Venereal Disease Research Laboratories (VDRL) study of CSF was nonreactive. Continued deterioration of mental state was evident and the patient was noted to intermittently confabulate. He rested in bed with his eyes closed and responded only to name.

On transfer of the patient to this hospital a physical examination showed normal vital signs and there was evidence that radical neck surgical procedures had been done several years before on the right. Patchy cutaneous pigmentation was noted in the left ophthalmic division of the trigeminal nerve. There was a nonradiating

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ABBREVIATIONS USED IN TEXT

ADH = antidiuretic hormone
CSF = cerebrospinal fluid
EEG = electroencephalogram
FTA = fluorescent treponemal antibody (test)
PML = progressive multifocal leukoencephalopathy
T_4 = thyroxine
TSH = thyroid stimulating hormone
VDRL = Venereal Disease Research Laboratories (test)

grade 2/6 systolic murmur at the left sternal border and the peripheral pulses were normal without detectable bruits. A prominent organic mental syndrome was present. This was characterized by orientation to person only, poor immediate and recent memory, and markedly decreased spontaneous speech. No aphasia was evident and he was able to follow only simple commands.

Neurological examination disclosed diffuse wasting and lead-pipe rigidity in the extremities. Symmetrical hyperreflexia was evident and the right plantar response was extensor, the left flexor. The patient was unable to walk or maintain his balance while seated. Positive glabellar, suck, snout and grasp reflexes were elicited bilaterally. The laboratory examination included a complete blood count with a leukocyte count of 9,100 cells per cu mm (92 segmental, 2 band forms, 1 lymphocyte and 5 monocytes). Studies of blood electrolytes on admission showed a sodium level of 122 mg per 100 ml, with a low serum osmolarity in the face of a high urine osmolarity. Blood urea nitrogen, calcium and glucose values were within normal limits. An x-ray study of the skull essentially showed no abnormalities except for an asymmetrical calcification in the left lateral ventricular area presumed to be a unilateral choroid plexus calcification. On repeat lumbar puncture there was clear, colorless fluid with a normal opening pressure; there was a protein level of 98 mg per 100 ml, a glucose value of 63 mg per 100 ml (simultaneous blood glucose value was 121 mg per 100 ml) and a negative VDRL test and a fluorescent treponemal antibody (FTA) study. There were 22 leukocytes, 100 percent lymphocytes and a cytologic examination for malignant cells was negative. Gram stain, routine cultures, fungus cultures and acid fast cultures were negative. CSF herpes simplex titer was 1:4; varicella-zoster 1:4. An electroencephalogram (EEG) done on the third hospital day showed a delta grade II, diffuse dysrhythmia. Findings on a repeat EEG one week later were essentially unchanged. The patient lay rigidly in bed with the eyes closed and pronounced flexion dystonia of the hips developed.

Results of repeat lumbar punctures showed a lymphocytic pleocytosis, elevated protein levels in the range of 100 mg per 100 ml and glucose values ranging slightly above 50 percent of the simultaneous blood glucose value. Cytologies, cultures and smears of the CSF were consistently negative. The patient's condition continued to deteriorate and he became unable to recognize his wife or sister. Skin tests for tuberculosis, candida and coccidioidomycosis were negative. An EMI® scan three weeks after admission showed mild cerebral atrophy. The thyroid stimulating hormone (TSH) level was 4.2 (normal) and the thyroxine (T_4) level was 1.4 μg per 100 ml. Therapy with sodium levothyroxine (Synthroid®), 25 μg per day, was started with no evident improvement in the clinical state. Despite fluid restriction, the syndrome of inappropriate antidiuretic hormone (ADH) secretion could not be corrected. CSF serologies were negative for cryptococcosis, aspergillosis, blastomycosis, candidiasis and coccidioidomycosis, and positive for histoplasmosis at 1:16. Convalescent CSF viral titers showed herpes simplex 1:4; varicella-zoster 1:64. A seven-day course of prednisone, 40 mg per day, was given but no neurologic improvement occurred. The patient died on the 52nd hospital day presumably of aspiration pneumonia.

Differential Diagnosis

JAY H. ROSENBERG, MD:* The patient is an 81-year-old man in whom nasopharyngeal carcinoma previously had been irradiated and in whom herpes zoster ophthalmicus developed. These events were followed by a progressive diffuse cerebral disorder. The striking positive laboratory findings in this case are three:

(1) The CSF herpes zoster titer rose from 1:4 on admission to 1:64 in the convalescent period.

(2) The patient was noted to have a low serum sodium level with a low serum osmolarity in the face of a high urine osmolarity. Inappropriate antidiuretic hormone secretion is the most likely condition to account for this combination of findings. Treatment could not fully correct

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the osmolarity and an x-ray study of the chest did not show the presence of a neoplasm. Findings on thyroid function tests were also found to be low with an initial T_4 value of 1.4 μg per 100 ml and a normal TSH level of 4.2.

(3) There was a persistent spinal fluid lymphocytic pleocytosis which is indicative of an inflammatory process involving the central nervous system.

A seven-day course of prednisone, 40 mg per day, was given in the terminal portion of the illness but there was no improvement and the patient died.

With a rise in the spinal fluid herpes zoster titer, could this entire process be explained as herpes zoster encephalitis? Generally, this uncommon disorder presents with a syndrome characterized by headache, ataxia, convulsions and coma.[1,2] In the acute stage there is usually a pronounced lymphocytic pleocytosis in the spinal fluid and cell counts of 60 to 450 are not unusual. Fever is frequently present; the spinal fluid protein level may be variable and viral cultures are commonly negative. In this patient, fever and convulsions were conspicuously absent. Certainly the diffuse encephalopathy could have been caused by herpes zoster meningoencephalitis. However, I would like to postulate that herpes zoster meningoencephalitis would not explain all the features of the patient's condition. There were, in addition to focal and diffuse neurological findings, inappropriate ADH secretion and involvement of the hypothalamic-pituitary axis.

The syndrome of inappropriate ADH secretion may be seen in the presence of encephalitis. In 1968, White and associates[3] reviewed their experience with St. Louis encephalitis in 52 patients. In this group, 18 of the 52 patients had an inappropriate ADH syndrome during their acute illness. It was concluded that the inappropriate ADH syndrome was an indication of some abnormality directly involving the brain parenchyma. Inappropriate ADH syndrome may be a nonspecific reaction to a wide variety of central nervous system diseases. Certain tumors may secrete ADH—the most common being oat cell carcinoma of the lung. However, in this patient findings on an x-ray study of the chest were negative, which would speak against the presence of a lung neoplasm. Although inappropriate ADH syndrome may be a nonspecific response, the presence of secondary hypothyroidism as a complication of viral encephalitis is exceedingly unusual. In their review of St. Louis encephalitis, White and associates[3] found that function of the pituitary-hypothalamic axis was undisturbed. The only change in the pituitary function is related to a general nonspecific stress reaction to the infection. Therefore, one could raise the possibility of an intraparenchymal process to account for the secondary hypothyroidism. If herpes zoster meningoencephalitis cannot account for all aspects of the condition, what are some alternative diagnostic possibilities?

With the past history of nasopharyngeal carcinoma, one must be concerned about the possibility of recurrent tumor. This commonly presents in the form of a locally invasive tumor with contiguous spread from the nasopharynx into the clivus or one of the sinuses to invade the brain. Generally, the presenting symptom is a progressive cranial neuropathy. In this patient there were no cranial nerve signs and, furthermore, no bony erosion was shown on x-ray films of the skull. Tomograms of the skull base would be helpful in excluding this diagnostic possibility. We are told that the EMI scan findings were normal but the EMI scan is less accurate in showing lesions at the base of the brain than supratentorial lesions.

One might raise the possibility of a carcinomatous meningitis but this is unlikely in view of the negative spinal fluid cytologies. Next, one must raise the possibility of some other type of infection with progressive diffuse involvement of the brain. The possibility of a brain abscess could be briefly considered, especially in the light of the persistent pleocytosis. However, against this are the normal brain scan findings, normal EMI scan results and the fact that the process was too diffuse. Could there have been multiple embolic infarctions from subacute bacterial endocarditis? This is a possibility in light of the fact that a heart murmur was noted at the time of this patient's admission but the time course was too long and fever was definitely lacking.

Could a tuberculous or fungal meningitis have been present? These are distinct possibilities but both skin tests and CSF cultures on several examinations were consistently negative for acid fast bacilli making tuberculous meningitis less likely. A thorough search was made for fungal meningitis; however, the CSF cultures were repeatedly negative and CSF serologies for cryptococcosis, aspergillosis, blastomycosis, candidiasis and coccidioidomycosis were negative. Further

evidence against the latter diagnoses was the presence of a normal CFS glucose value, which is usually but not invariably decreased in these chronic infections.

What other possibilities might be considered? Progressive multifocal leukoencephalopathy (PML) is another diagnostic consideration. The patient does have the background of preexisting carcinoma. In PML the involvement is commonly diffuse and asymmetric but usually involves the cerebral hemispheres and not the brain stem. This patient had both brain stem and hemispheric involvement. Absent was any visual impairment which is usually an early symptom in the course of PML. Other common findings include focal neurological deficits and an organic mental syndrome as was seen in this patient. However, against the diagnosis of PML is the fact that the pleocytosis is extremely unusual in this disease. The EMI scan in PML has been reported to show low density, asymmetrical lesions in the subcortical white matter that lack contrast enhancement.

If we have ruled out infection, recurrent tumor and PML, what other diffuse processes can one postulate that might be associated with herpes zoster in this patient? An intracranial arteritis or vasculitis certainly could explain this patient's deteriorating course. The association of a persistent spinal fluid pleocytosis and encephalopathic features raises this possibility. In the classification of vasculitis one must consider infection which has already been discussed. Other vasculitides include collagen-vascular disorders of which systemic lupus erythematosus is the most common, and necrotizing angiitis. Within the latter category are periarteritis nodosa, temporal arteritis and granulomatous giant cell arteritis of the brain. Other miscellaneous arteritides would include radiation vasculitis. Systemic lupus erythematosus presents with primary widespread involvement of the organs and is later followed by central nervous system complications. Personality change, confusion, organic mental syndrome and convulsions may be encountered in central nervous system lupus erythematosus. A cranial neuropathy may be seen but a peripheral neuropathy is more common. CSF pleocytosis may occur in systemic lupus erythematosus but one would expect systemic involvement including evidence of bone marrow and renal disease. Commonly periarteritis nodosa presents with headache, fever, skin rash, arthralgias, nasal symptons, coughing, wheezing, chills and night sweats. A skin rash and subcutaneous nodules are often present. Peripheral neuropathy is the most common neurological complication of periarteritis. In addition to the neuropathy, there may be central nervous system involvement in such cases but usually there are systemic findings of hematological and renal involvement. Aneurysmal dilatations or segmental occlusions of cerebral blood vessels may be seen in many of the vasculitides. We have no knowledge of the presence of aneurysmal dilatations due to the lack of information about this patient's blood vessels. In this patient a cerebral angiogram might have been a fruitful diagnostic procedure in that it might have shown either small vessel occlusion or aneurysmal dilatations of blood vessels.

The possibility of radiation-induced vasculitis affecting the major vessels at the base of the brain must be raised. The ports of radiation therapy in treating tumors of the nasopharynx may not be precise and scatter of irradition is possible. In one report, a fatal foam cell arteritis developed in a patient with Hodgkin disease following nasopharyngeal irradiation.[4] In that patient there was pronounced involvement of the hypothalamus and circle of Willis with the arteritis. The late delayed effects of radiation commonly occur between one and five years after treatment. Radiation arteritis is therefore a distinct possibility in the patient discussed today who previously received 7,000 rads of irradiation to the head region.

In the literature there has also been an association of herpes zoster with granulomatous giant cell arteritis of the nervous system.[5-7] Granulomatous arteritis is a necrotizing angiitis with the typical pathological signs in the blood vessels characterized by a granulomatous inflammation and giant cells. This condition commonly is characterized by headache, mental change, focal neurological abnormalities and spinal fluid pleocytosis.[8,9] Although this condition almost exclusively involves the intracranial vessels, the pathology is quite similar to temporal arteritis.

In summary, the progressive neurological disorder in this patient was most likely the result of an intracranial arteritis associated with herpes zoster, perhaps due to granulomatous angiitis or irradiation.

Pathological Discussion

DR. SIPE: The findings at general postmortem examination included bilateral bronchopneumonia due to aspiration, fibrosis of the thy-

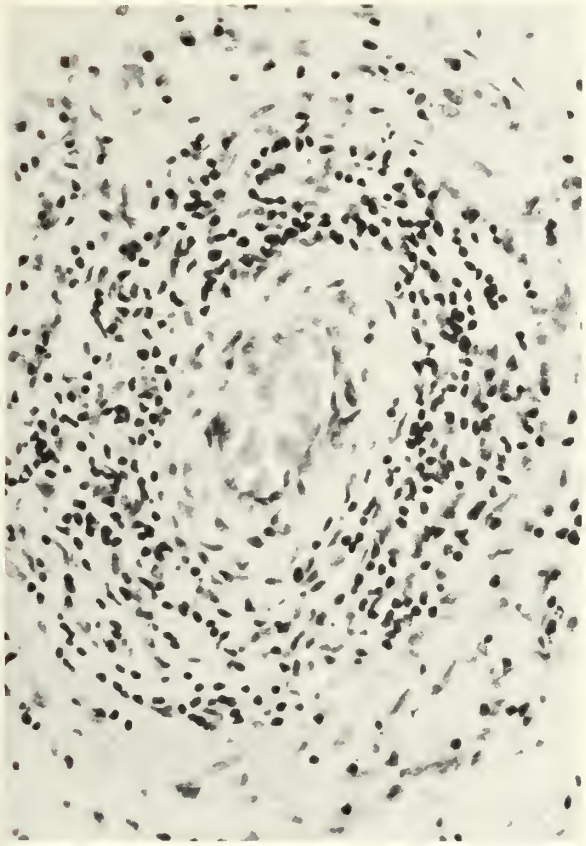

Figure 1.—This small vessel in the basal meninges illustrates the widespread findings of vasculitis. The angiitis is characterized by infiltration of the vessel wall with numerous lymphocytes, thickening of the tunica media and narrowing of the vascular lumen. (H & E×300)

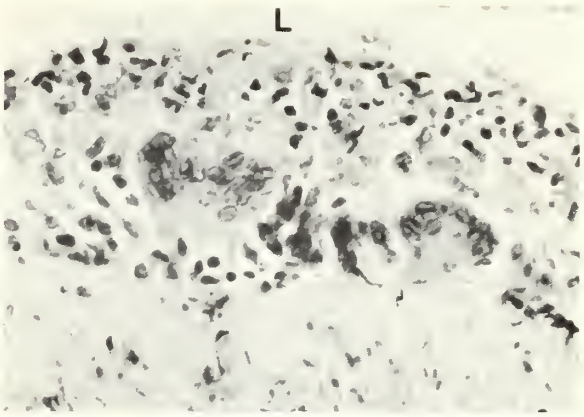

Figure 2.—Higher magnification view of a severely involved artery showing a cluster of multinucleated giant cells in the region of the vascular intima and internal elastic lamina. The area surrounding the giant cells is infiltrated by lymphocytes and histiocytes. L indicates vascular lumen. (H & E×350)

roid gland and bilateral renal cysts. There was no evidence of recurrent or metastatic squamous cell carcinoma of the right tonsillar region. Microscopic examination of the organs, skin and skeletal muscle showed no inflammatory lesions save for the aspiration pneumonia.

The brain weighed 1,550 grams in the fixed state. The leptomeninges were diffusely thickened, fibrotic and opaque at the base of the brain, as well as over the convexities. The great vessels of the circle of Willis were enmeshed in the thickened meninges but there were no atherosclerotic plaques and the large vessels appeared otherwise grossly normal. Serial coronal sections through the cerebral hemispheres, cerebellum, brain stem and spinal cord disclosed multiple areas of softening and cavitation in the striatum and internal capsule bilaterally, the head of the left caudate nucleus, both thalami and especially in the dorsomedial and anterior nuclei bilaterally. Diffuse neocortical atrophy and mild enlargement of the ventricular system were present.

On microscopic examination of the basal leptomeninges and the meningeal vessels, there was the entire spectrum of necrotizing granulomatous angiitis, principally involving small and medium sized arteries (Figure 1) in a focal and patchy manner but also occasionally involving large arteries. In the involved vessels there was invasion of the adventitia, media and internal elastic lamina by lymphocytes, plasma cells and histiocytes together with accumulation of numerous giant cells in many involved arteries (Figure 2). Thrombosis and recannilization of many vessels was a prominent feature (Figure 3). Stains for bacteria, fungi and acid fast bacilli in involved vessels were negative. Elastic arterial stains showed complete disruption of the internal elastic lamina confirming the necrotizing character of the angiitis. Numerous old and recent ischemic infarctions were present in the neostriatum, thalamus, internal capsule and hippocampus on both sides. Active granulomatous arteritis together with thrombosed and recannilized arteries were evident in many infarcted zones especially in the putamen. There was no microscopic evidence of a systemic arteritis in any of the organs, skin or skeletal muscle. Therefore, results of the gross and microscopic neuropathological examinations, as well as the clinical and laboratory findings, support the diagnosis of granulomatous giant cell arteritis of the central nervous system.

This syndrome has been of considerable interest since the early reports of Wolfe and New-

Figure 3.—A medium sized meningeal vessel illustrating thrombosis of the lumen together with an active vasculitis and multinucleated giant cell accumulation (arrows). (H & E×130)

man[10] and Cravioto and Feigen.[11] The distinctive pathological features are the striking predilection for the central nervous system without evidence of angiitis elsewhere. In most reported cases, a noninfectious granulomatous angiitis involves small and medium sized arteries. This distinguishes the disease from many other forms of vasculitis that may simultaneously involve both intracranial and extracranial vessels. A highly focal and random pattern in the central nervous system with predilection for the meningeal vessels, vessels of the cerebral cortex, basal ganglia and spinal cord has been reported.[6-12] Histologically, most reported cases are quite similar to the present case.

The cause and pathogenesis remain completely unknown despite several recent reports. Although the granulomatous inflammation suggests invasion by microorganisms, none have been identified.[13] The angiitis resembles histologically that seen in temporal arteritis and allergic granulomatosis.[13] The present disease can be distinguished because the angiitis is almost exclusively confined to the central nervous system. Several reported cases of granulomatous giant cell angiitis of the CNS have been associated with lymphoreticular malignancies and herpes zoster infection.[5-7] The association of herpes virus infection and giant cell granulomatous arteritis is of particular interest because of the well known ability of viruses to induce the formation of syncitia in tissue culture. This suggests a possible mechanism for multinucleated giant cell development. Electron microscopic studies seeking virus-like particles are limited to the study of Reyes and associates[14] who found intranuclear "virus-like" particles in glial cells from a formalin-fixed postmortem brain specimen. However, to be convincing the latter study's findings must await confirmation by other techniques such as immunofluorescent staining or viral isolation because of the well known difficulties encountered in the interpretation of "virus-like" particles in postmortem brain specimens.[15]

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Refer to: Chronic lymphocytic leukemia—Medical Staff Conference, University of California, San Francisco. West J Med 127:221-228, Sep 1977

Chronic Lymphocytic Leukemia

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and Robert C. Siegel, Associate Professor of Medicine and Orthopaedic Surgery, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *It has been our custom to ask our chief medical residents at Moffitt Hospital to discuss a topic at Medical Grand Rounds near the conclusion of their residency year. We have been privileged to have Dr. Janet Abrahm as chief resident during this past year. She will discuss the topic of chronic lymphocytic leukemia.*

DR. ABRAHM:† The first description of leukemia was published simultaneously in 1845 by Craigie in Edinburgh and Virchow in Berlin. In 1905 acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL) and "myelogenous" leukemias were first officially distinguished. The process of discovering and defining the different types of leukemic cell is still continuing. Before describing to you some of what we know about the leukemic cell in CLL, I would like to briefly review the characteristics and functions of normal T and B cells.[1,2]

T, or thymus derived, cells are distinguished from B, or bone marrow derived, cells by immunologic characteristics. The former make up most of the circulating lymphocyte population and are located in characteristic areas of lymph nodes and spleen. Their functions are still being discovered, but it is felt, from studies in patients devoid of them, that T cells (1) are key mediators of cellular immune responses, including delayed hypersensitivity reactions, (2) may modulate B cell responses to antigens both as facilitators, so called "helper" T cells, and possibly as inhibitors, so called "suppressor" T cells. Patients without functional T cells, therefore, are prone to fungal, parasitic and intracellular bacterial infections. Their role in viral disease is still unclear, although they are clearly involved in the response to viruses that spread directly from cell to cell, such as in herpes zoster.

B cells are major antigen recognizers and antibody producers. Patients who lack them are plagued by extracellular bacterial infections, as most bacteria must be coated by opsonizing antibody in order to be subject to optimal phagocytosis and clearing from the blood stream. Antibody also seems to affect the infectivity and dissemination of several viruses by inhibiting attachment, penetration or replication, especially of those that produce systemic infection.

In patients with CLL there remain some functional, normal B cells and a normal T cell pool.[3,4] But the leukemic B cell is the predominant cell in 98 percent of the cases of CLL. Moreover, it now seems clear that CLL is due to the proliferation of

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†Janet L. Abrahm, MD, Chief Resident.

ABBREVIATIONS USED IN TEXT

ALL = acute lymphocytic leukemia
AIHA = autoimmune hemolytic anemia
CLL = chronic lymphocytic leukemia
CLSL = chronic lymphosarcoma cell leukemia
DNA = deoxyribonucleic acid
HL-A = histocompatibility locus A
ITP = idiopathic thrombocytopenic purpura
SLE = systemic lupus erythematosus

one clone of cells. The surface immunoglobulin produced by the malignant cells of CLL has been shown to be monoclonal, with single antibody specificity and single idiotype (variable region).[5,6] The cells of CLL are structurally and functionally abnormal in several ways (including different specificity of C_3 receptors, different scanning EM morphology) but the most clinically significant abnormalities involve their immunologic responsibilities. *In vitro,* the cells have delayed antibody secretion and delayed, if any response, to normal mitogens. *In vivo* studies in patients with CLL show an inability to produce antibodies to new antigens, to remember old antigens and produce antibodies to them, and to develop a delayed hypersensitivity response to an antigen to which the organism had not previously been exposed. Significantly, the delayed hypersensitivity (skin test) response to old antigens is retained.

How might we explain these *in vivo* findings? Figure 1 schematically illustrates what happens to the lymphocyte pools in a patient with CLL. The sizes of the normal B and T cell pools remain unchanged, but the total pool size is greatly increased by the leukemic B cells. In addition, the presence of the abnormal B cells in the lymph nodes and splenic channels may impair contact between T cells and B cells. Moreover, the leukemic B cells may have receptors for the normal T cells, and so, by competitive inhibition, interfere with normal T-B cell interaction. This functional dilution of T-B cell interaction might explain the observed inability to produce antibody to new antigens. The dilution of normal T or B cells themselves in the lymph nodes and spleen might sufficiently decrease contact with new or old, frequently occurring antigens so as to lead both to impaired ability to mount a hypersensitivity response to a new antigen and to a general decrease of antibody production. This might then explain the hypogammaglobulinemia found in the majority of patients with disease of greater than five years. The standard skin tests remain positive, however, because the previously sensitized, circulating T cell interacts normally with its antigen and the skin macrophage. In sum, then, the leukemic B cell is an immunologically incompetent and long-lived cell, which may, by its accumulation and dilution of the normal T and B cell interactions, lead to the alterations in immunocompetence seen in patients with CLL.

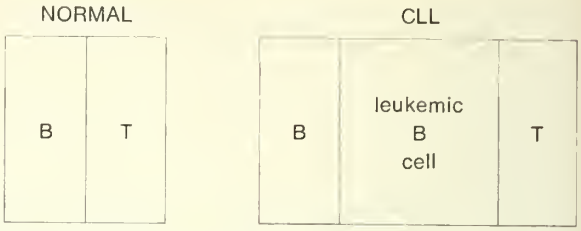


Figure 1.—Proposed dilution of normal B cell and T cell interactions by leukemic B cells of chronic lymphocytic leukemia (CLL).

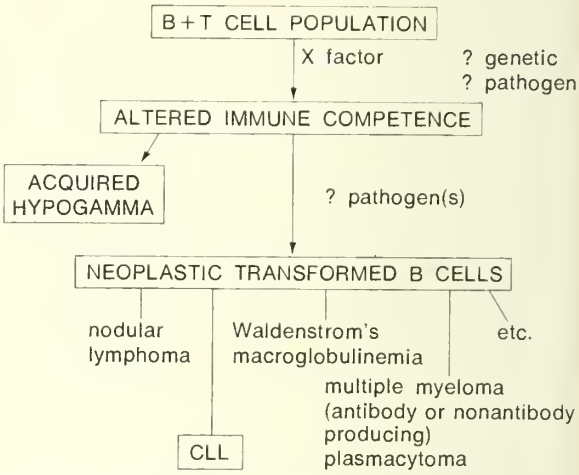


Figure 2.—Postulated range of B cell disorders including chronic lymphocytic leukemia (CLL).

The cause of CLL is unknown. One might, however, postulate a defect producing a range of B cell disorders of function (see Figure 2). For example, in the acquired hypogammaglobulinemic state, a defect of release of gamma globulin has been detected, but this does not progress to neoplasia (even though the patients do have intestinal nodular hyperplasia). The same alteration (for example, an inherited defect or an environmental pathogen, or both) might lead to neoplastic transformation in B cells of different types or stages, with the observed clinical syndrome resulting from the functional capabilities of the particular cell which has been transformed.

A genetic susceptibility to B cell disorders of this kind has been suggested by studies of families in whose members lymphatic leukemias or lym-

phomas developed at an unusually high frequency.[7] In these families, those siblings in whom the leukemia or lymphoma did not develop do have abnormalities of immunoglobulin production. Furthermore, there is an increased incidence of leukemia in patients with x-linked agammaglobulinemia. The susceptibility to malignancy could be simply due to the neoplastic transformation itself, or more likely to the immunologic defect, resulting in increased susceptibility to an environmental carcinogenic agent or loss of immunologic surveillance giving rise to the establishment of neoplasia.

Returning to CLL, let us now discuss some more general considerations: CLL accounts for 25 percent of all leukemias. It is more commonly reported in whites than blacks, most commonly among Jews and relatively rarely among Asiatics. The male to female ratio is 2:1. The disease is rare in persons under 40 years of age. Eighty percent of new diagnoses are made in patients over 50.

My discussion of the clinical syndrome will include the following areas: infiltrative manifestations, immunologic phenomena, infections, second malignancies and causes of death. We will then discuss prognosis and therapy. Because the infiltrative manifestations are those that most commonly bring the patient to the doctor, we shall begin with them. Of these, the most common presenting *symptom* in all series is enlarged lymph nodes, although CLL is an accidental *finding* on routine complete blood counts in an equal number of patients.[8] The other initial symptoms include those of anemia in 25 percent of patients and sweating and weight loss in 20 percent. Fever, complications secondary to enlarged liver or spleen, cutaneous or mucosal hemorrhage and itching each were noted in about 10 percent.

Diffuse lymph node enlargement is also the most common physical finding (63 to 89 percent) on initial presentation. The nodes are often small, discrete, firm and freely movable, increasing in size as the disease progresses. Node compression, especially in the mediastinum or retroperitoneal areas, can lead to bronchial or other obstructive symptoms or, more rarely, a superior vena cava syndrome or aphonia from recurrent laryngeal nerve compression.

Splenomegaly is present in about half of the patients, and hypersplenism, splenic infarction, subcapsular bleeding and perisplenitis can occur if the splenomegaly is massive.

The bone marrow in untreated patients is hypercellular and infiltrated by lymphocytes. At diagnosis, a lymphocyte count greater than 60 percent is found 94 percent of the time and will increase to 80 to 100 percent terminally. Bone marrow function, however, is usually good throughout most of the course, though in a significant number of cases, marrow failure, with refractory anemia and thrombocytopenia may supervene.

Organ infiltration by the leukemic cells has been reported in almost every system. That in the liver, kidney, endocrine organs, esophagus and gastrointestinal tract is usually asymptomatic. That into the salivary and lacrimal glands can produce xerostomia and xerophthalmia (in contrast, note that the infiltrate in Sjögren syndrome is polyclonal and stains for B cells). In the skin, exfoliative erythroderma is seen along with tumors, especially of the face, and infiltrated plaques.

Pleural effusions are not an infrequent finding, whereas an actual lung infiltration is rare. Central nervous system manifestations include the more common herpes zoster, along with the rare cranial nerve palsy and spinal cord compression. The bone lesion is most typically generalized osteoporosis, but steroid responsive hypercalcemia with normal parathyroids has been reported. Other rare findings include glaucoma secondary to limbic infiltration, and acropachy—that is, finger clubbing with symmetrical destruction of terminal phalanges secondary to subungual infiltration.

Weight loss is seen not infrequently late in the course of disease in these patients. While it is probably not due to infiltration into the gastrointestinal tract, there may be more to it than the "hypermetabolic state." Malabsorption in patients with CLL was documented in 1960.[9] In macroglobulinemia, the malabsorption has been felt to be secondary to deposition of Bence-Jones amyloid in the extracellular spaces,[10] but this has not been seen and would not necessarily be expected in CLL where the paraprotein production is much less. Hypogammaglobulinemia, however, as stated above, *is* common in CLL. Diarrhea with malabsorption is seen in other such states and in these states is found to be secondary to giardia infestation. In the reported cases of CLL with malabsorption, giardiosis was not looked for and levels of gamma globulin were not reported. These

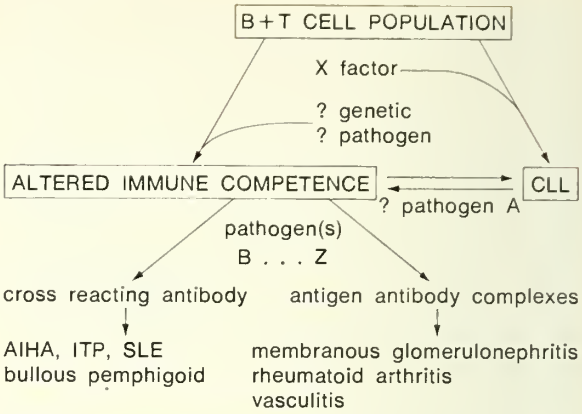
studies would seem to be the logical next step in elucidating the mechanism of the malabsorption in the CLL patients.

Next, let us turn to the associated immunologic phenomena, as herein lies one of the paradoxes of this disease. As mentioned before, the leukemic cells poorly synthesize antibody and, in fact, the gamma globulin levels often fall as the disease progresses, and yet an assortment of antibody mediated complications occur.[8] The CLL cell products do not seem to be responsible. An IgM spike is found in less than 10 percent of patients, and in all cases where it has been examined it is identical to that on the leukemic B cell surface. It does have anti-human IgG activity,[11] but it has never been shown to have anti-red cell, anti-platelet or anti-nuclear specificity. Furthermore, as it is an IgM, not an IgG, one would not expect it to cause the observed Coombs' positive hemolytic anemia. In fact, it probably only produces trouble as a cryoglobulin, and that rarely.

Allergic phenomena are retained in CLL (for example, allergies to penicillin and other medications) but this is most likely due to the retained normal B cells. Anaphylaxis (to gamma globulin injections, for instance) also can occur, but this is a T cell and IgE mediated phenomenon and could be explained by retained low rates of IgE production. Patients also have severe reactions to mosquito bites, and, occasionally, to skin tests.

Autoimmune hemolytic anemia (AIHA) is found in 25 percent of patients, and other reported associated phenomena include idiopathic thrombocytopenic purpura (ITP), systemic lupus erythematosus (SLE), pure red cell aplasia,[12] bullous pemphigoid[13] and thyroiditis, as well as rheumatoid arthritis, vasculitis and membranous glomerulonephritis with nephrotic syndrome.[14]

The causes of the autoimmune and so-called collagen diseases are, of course, unknown, and it is very possibly folly on my part to try to find relationships between two processes, the causes of both of which are unknown. However, we can say that any theory explaining the unusual concurrent incidence of autoimmune disease and CLL will have to explain both the relative selectivity of the immune abnormalities, and also the often independent courses of the CLL and the autoimmune disease in the same patient. There may be an inherited predisposition to both diseases, or susceptibility induced by some characteristic of one disease may lead to acquisition of the others (or both). Again, as when I discussed the pathogenesis of CLL itself, I find myself invoking the presence of a genetic susceptibility, with or without an effect from those elusive environmental pathogens.



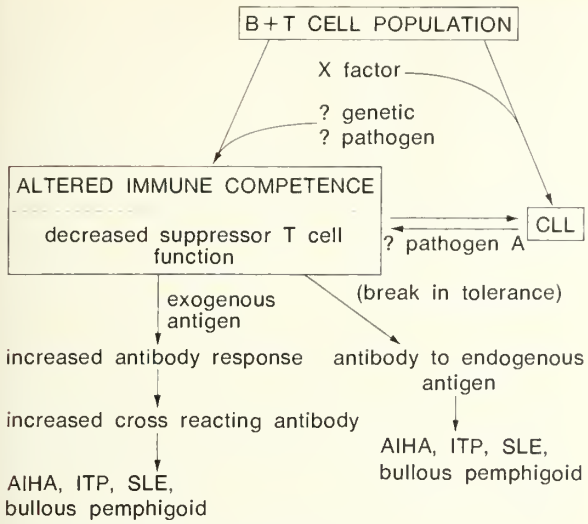
AIHA = autoimmune hemolytic anemia
ITP = idiopathic thrombocytopenic purpura
SLE = systemic lupus erythematosus

Figure 3.—Theory of relationship between chronic lymphocytic leukemia (CLL) and frequently accompanying immunologic disorders.

First, let us consider genetic susceptibility to both diseases, as this possibility is suggested by a very interesting mouse model.[1] In inbred mice, the histocompatibility complex, H-2, includes genes that code for the transplantation antigens as well as those that determine the magnitude and immunoglobulin class of antibody produced in response to specific immunogens, the susceptibility to leukemia viruses and the intensity of cell-mediated immune responses.

In humans no such immune response region has yet been characterized, but in cultured lymphocytes the level of antibody production to streptococcal antigen has been shown to have a histocompatibility locus A (HL-A) association; and single HL-A loci have been associated both with allergic, and with autoimmune phenomena. In each of the family studies of CLL there was, in addition to the unusually high incidence of CLL among the siblings, frequently a sibling or daughter without CLL but with clinical rheumatoid arthritis, rheumatic fever, joint disease, atopic skin disease, anemia or thrombocytopenia.

Now to explore the second theory. The top row of the diagram in Figure 3 simply represents a synthesis of the theories I mentioned regarding the cause of CLL. That is, either a creation of immune deficient state via genetic or environmental forces, or both, which then led to CLL, or vice



AIHA = autoimmune hemolytic anemia
ITP = idiopathic thrombocytopenic purpura
SLE = systemic lupus erythematosus

Figure 4.—Theory of relationship between chronic lymphocytic leukemia (CLL) and immunologic disorders involving abnormal T cell function.

versa. In either event, altered immune competence clearly is *present* in CLL. All I have added, then, is some different pathogens, working in this immunologically deficient milieu, leading to the autoimmune phenomena. In patients with congenital or acquired hypogammaglobulinemia, who do not have CLL, there is an increased incidence of rheumatoid arthritis-like disease, systemic lupus erythematosus, idiopathic thrombocytopenic purpura and hemolytic anemia. Moreover, the arthritis often resolves when gamma globulin injections are given. The autoimmune hemolytic anemia then might be a deleterious by-product of an inappropriate response to an environmental pathogen. There is certainly an association noted in otherwise healthy persons of autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura following viral infection; and in other species, viruses have caused blood group-type antigens to appear on the infected cells. The immune incompetence in CLL could be simply widening the range of viruses capable of inducing such phenomena in humans. The rarely reported rheumatoid arthritis, vasculitis and membranous nephropathy may be secondary to circulating antigen/antibody complexes produced by a poorly cleared viral infection. The fact that IgG therapy may reverse the arthritis in x-linked hypogammaglobulinemia patients suggests that the response is secondary to clearing of such an infection.

The T cell arm of regulation may also be out of balance in the immunodeficiency state. In Figure 4 "decreased suppressor T activity" has been added to emphasize the effects this alone might produce. The helper T cell population is felt to be normal in CLL, but there are no studies at present of the activity of the suppressor T cells in CLL. Should *their* activity or contact with normal B cells also be diminished through dilutional effects in the lymph nodes, spleen or other parts of the circulation, or should the leukemic B cells prove to have receptors for these T cells as well, antibody production to common antigens, exogenous or endogenous, might be excessive or inappropriate. Mice which acquire autoimmune hemolytic purpura, systemic lupus erythematosus-like renal lesions and dermatitis if thymectomized at birth, in fact, do not get them if raised in a germ free environment.[15] The autoimmune hemolytic anemia in man, then might be the product of crossreacting antibody produced in excessive amounts to some pathogen. Normal human B cells have receptors capable of reacting with antigens such as deoxyribonucleic acid (DNA) and thyroglobulin. That they usually do not suggests they ordinarily are suppressed. The systemic lupus erythematosus, thyroiditis or even autoimmune hemolytic anemia then might be due to a break in this immunologic tolerance. There is some indirect evidence that the suppressor T cells are not, in fact, functioning up to par, at least in the suppression of cell-mediated immunity, since, as you recall, in CLL patients there frequently are excessive delayed hypersensitivity responses to mosquito bites and skin tests.

The reverse hypothesis (that is, that chronic stimulation of antibody production leads to CLL, such as seen in New Zealand Black mice whose lymphoreticular disorders are always preceded by multiple immune phenomena) seems not to apply. The autoimmune phenomena in CLL can precede or follow the appearance of the disease, and the courses even when simultaneous are independent.

Returning to more practical considerations, consider the infections in patients with CLL. Infection is the major cause of morbidity and mortality in patients with CLL. The infectious agents are most commonly bacterial, especially those requiring antibody for optimal clearance. Pneumococci and staphylococci predominate, followed by Escherichia coli, Proteus, Pseudomonas and streptococci. Cryptococcal infection, especially of the central nervous system is increased, and toxo-

plasmosis and pneumocystic infection are also being reported. Herpes zoster is the most common serious viral pathogen.

The best correlation with the increased susceptibility to infection in these patients is the level of gamma globulin. The exact cause of the hypogammaglobulinemia is uncertain. As in other hypogammaglobulinemic states, the half-life of the globulin is prolonged rather than shortened. Contributing factors might include those mentioned before, such as decreased antigen contact with the diluted normal B and T cells, or lessened helper T cell contact with B cells, or T cell "binding" by the leukemic B cell. Miller and Karnofsky found that a gamma globulin level of 0.7 mg per dl or less was uniformly found in those patients in whom recurrent infection was a problem. As you recall, hypogammaglobulinemia is present in most patients with disease of greater than five years' duration. The hypogammaglobulinemia is irreversible, despite improvement in other factors with therapy.

It seems, however, that there must be in CLL other immune derangements contributing to the high infection rate since in patients with congenital hypogammaglobulinemia there are much lower infection rates with comparable globulin levels. Steroid therapy is not the only culprit; the patients in the series mentioned had an increased incidence of infection before steroid therapy was begun. No abnormality of the secretory immunoglobulin system or alternate complement pathway has been defined. The inflammatory exudate has also been examined, and both leukocytes and macrophages are normal in number. However, leukocytes require antibody coating of bacteria for optimal phagocytosis, and macrophages require products of activated lymphocytes for their optimal activity. The functional capabilities of both these cells may be reduced when the nonantibody producing, and nontransformable B cell of CLL dilutes the normal one.

T cell function is probably normal, which explains the general lack of problems with intracellular pathogens and most viruses but leaves another mystery, that of the increased incidence of both zoster infection and dissemination. The age expected incidence of zoster infections is 1 percent, and yet it is found in 13 percent of patients with CLL. Zoster appears more frequently in sites of tumor infiltration or trauma and is significantly increased in irradiated areas.[17] There is no correlation with immunosuppressive therapy (surgical: splenectomy or thymectomy; medical: azathioprine, prednisone, actinomycin), hypogammaglobulinemia or leukopenia.

A similar type of viral behavior is seen in a virus of E. coli K-12, lambda bacteriophage. Lambda bacteriophages have been shown to enter the genome of the host cell (E. coli K-12) and multiply only as the cell itself does unless exposed to ultraviolet light, x-ray or nitrogen mustard. If such an exposure occurs, induction follows with rapid multiplication of phage and subsequent host cell destruction. Studies investigating the question of herpes virus integration into the human genome are now underway. Furthermore, when a CLL patient has an attack of zoster, there is a higher chance it will disseminate. Antibody levels do not correlate with dissemination, but vesicular interferon levels do have a delayed rise in those patients who disseminate.[18] It may be true here also that the lack of products of activated lymphocytes impairs macrophage function, leading to the dissemination (there are normal macrophage numbers at the bases of the vesicles). In any event, even in CLL dissemination usually is self-limited, lasting only three to four days, and usually without serious consequences.

There is an increased incidence of second malignancies in patients with CLL.[8] Most of this is accounted for by an 8- to 12-fold increase in skin cancer, with only a 2-fold increase in other types of cancer. Many types of malignancy have been reported, but their incidence does not seem to match that in the general population. A lack of "immune surveillance" would not explain this peculiar skewing. Moreover, there is no significant correlation here with hypogammaglobulinemia or autoimmune phenomena, and the helper T cells are normal. Acute leukemia is a rare complication and represents, in most cases, a second malignancy. There has been one report of a lymphoblastic leukemia developing in two patients with CLL, one of whose cells were studied. The lymphoblastic leukemic cells produced the same immunoglobulin as that present on the small CLL cells, suggesting an actual blastic transformation of the CLL cell.[19] In all but one of the other reported cases of superimposed acute leukemia, the patients had received radioactive phosphorus (^{32}P), alkylating agents or radiation therapy, or both. This association raises questions regarding safety of these therapeutic agents.

To complete the clinical picture, I should mention the causes of death in CLL. Infection is by

far the most common, followed by "other disease," cachexia—that wasting syndrome with a hypermetabolic state that occasionally supervenes —anemia and lastly hemorrhage, the latter representing only 3 percent.

Finally, we turn to considerations of therapy. In thinking about therapy for this disease, as in any other, it is essential to consider the natural course of the disease unmodified by therapy and the risks versus benefits of the therapeutic options. In CLL, this caution is especially relevant.

The natural course and prognosis of this disease is difficult to state. Most past studies have been hampered by several factors: (1) Before the era of routine complete blood counts, the disease was detected only after symptoms had developed. Today, too, younger people are subject to fewer routine screening procedures than older ones. (2) More fundamentally, the nature of the cell of classic CLL has only recently been elucidated. Before this, many other morphologically similar diseases, especially chronic lymphosarcoma cell leukemia (CLSL), which may have very different natural histories, were being lumped in with CLL series and affecting the survival data. Previous studies *have* shown that survival best correlates with how long the disease had been present symptomatically before the diagnosis was made and how many complications were present at the time of diagnosis. Rai and co-workers have formalized this into a proposed staging scheme.[20] Their data indicate that median survival in patients picked up accidentally is greater than 150 months. Survival in patients presenting with lymphocytosis and splenomegaly with anemia or thrombocytopenia, that is stage 3 and 4, is a median of only 19 months.

Therapy, too, has been difficult to evaluate, since therapies were not compared in groups with comparable stages of disease.[21] It seems the general conclusion is to keep in mind the philosophy of *do no harm*. Studies comparing patients treated infrequently or symptomatically with those treated regularly, irrespective of symptoms, showed no difference in survival rates. Indications for therapy include[22] bulky lymphadenopathy, symptomatic splenomegaly, autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura, marrow "failure," that is neutropenia, anemia, thrombocytopenia or hypermetabolic state with weight loss, sweating and the like.

Allopurinol, of course, should be given before beginning any therapy. As to chemotherapy, there is a virtual absence of good studies comparing different regimens. In the absence of hemolytic symptoms, chlorambucil can be used safely and will reduce lymphadenopathy and spleen size in 25 percent and decrease peripheral counts in 70 percent of cases. Usually the hematocrit and platelet count will not rise significantly, and the gamma globulin levels will remain depressed.

Steroids should be the first line of therapy in patients with autoimmune hemolytic anemia or packed marrow states, as alkylating agents may lead to a precipitous fall in the hematocrit before the process is brought under control. As soon as possible an alkylating agent should be added and the steroid tapered. Therapy with steroids in other patients is also useful; it shrinks the spleen and lymph nodes and decreases lymphocyte counts in the marrow even though the peripheral counts may rise initially. With the "unpacking" of the marrow, the hemoglobin, neutrophil and platelet levels seem to rise. In stage 3 and 4 disease a regimen of cyclophosphamide (Cytoxan®), vincristine and prednisone has clearly been shown to increase survival over that expected.

Several types of radiation therapy have been tried, but in general they are unpredictable in their effects on the blood counts in this disease and are therefore less safe. Local radiation therapy to leukemic masses may be used safely in most cases.[23] Mediastinal irradiation, however, has been shown to lead to severe depression of both neutrophil and lymphocyte counts, resulting in severe and often fatal infections.[8]

Both splenic and low-dose total body irradiation (150 to 300 rads)[23] have led to improvements in lymph node and spleen size, anemia and platelet counts, and even to complete remissions—again for unclear reasons. Even extracorporeal irradiation through a Scribner shunt has been efficacious in patients refractory to other therapy.[24] In addition to the cellular lethality of radiation and alkylator therapy, the question of their roles in the appearance of a second malignant process in CLL is an important one and may affect one's choice of therapeutic agent, especially in a young patient. The method with the best therapeutic index is leukapheresis[25]—simply taking off the excess lymphocytes, although this is a time consuming process for the patient.

For nonhemolytic anemia in patients for whom steroid therapy or radiation has not been of benefit, androgen therapy in large doses along with glucocorticoids has been reported to be of bene-

fit.[22] For the autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura, glucocorticoids and immunodepressants, if necessary, are obviously the first choice of therapy. In refractory cases spenectomy has been helpful and should be seriously considered. It should also be used for severe symptomatic hypersplenism.

Infection deserves yet another word. Prevention of infection by the usual commonsense measures, including keeping the patient out of hospital, decreasing local obstruction produced by enlarged nodes, does seem to help. Fever in this form of leukemia is usually of infectious origin, not secondary to the disease, and a vigorous search should be made for the cause. The types of infections, again, are most commonly pneumonia and furunculosis; the bacterial pathogens are usually the Pneumococcus, Staphylococcus, E. coli, Pseudomonas and Proteus. Cryptococcal meningitis should be looked for and zoster thought of in a patient complaining of radicular pain. At present there is no role identified for a zoster immune globulin in CLL patients, even those exposed to a child with varicella.[26] In a double-blind comparison with a placebo, interferon—if therapy is started early—has been shown to be useful in reducing pain and distal cutaneous spread. Adenine arabinoside for severe disseminated infection has provided some encouraging results in early trials. Some special cautions here: do not attempt to immunize these patients with live virus of any sort, as they may get severe local reactions and even generalized infections without significant antibody responses being achieved. The malabsorption problem may in fact be a giardia infestation, as proposed above. Pending further studies of this matter, I think that malabsorption should be looked for in a patient with diarrhea or weight loss and hypogammaglobulinemia. If it is present, a search for giardia should be made, and an empiric trial of therapy for giardiosis begun if no other cause appears.

In severe cases of hypogammaglobulinemia with recurrent infections gamma globulin has been of help[22] but in respiratory disease large doses may be necessary. Fresh frozen plasma, a source of IgM, may be useful in addition.

I have tried to provide an overview of CLL: some of the characteristic findings of the disease, some of the theories that try to explain these findings, and some practical management hints. I hope this information will prove of use in your understanding and treatment of patients with CLL.

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Important Advances in Clinical Medicine

Epitomes of Progress — Neurosurgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in neurosurgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in neurosurgery which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Neurosurgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Neurosurgical Treatment of Stroke

ADEQUATE TREATMENT of stroke depends on several factors: (1) early presumptive diagnosis of vascular insufficiency of the brain which precedes irreversible brain infarction (that is, a diagnosis of transient ischemic attack [TIA] or reversible ischemic neurological deficit [RIND]), (2) complete workup including cerebral angiography to show vascular stenotic or occlusive lesions that correlate with neurological symptoms and signs and (3) prompt and appropriate neurosurgical or medical treatment before irreversible significant brain infarction has occurred.

Early presumptive diagnosis of TIA or RIND reflects a careful history. Abrupt, possibly repetitive neurologic dysfunction has occurred followed by recovery which is usually prompt and complete. These episodes are most common in patients 50 to 60 years old who have arteriosclerosis. Hypertension may or may not be present. Orthostatic hypotension frequently is present. The neurologic defect will suggest the vessel involved. As an example, blurring of vision in the left eye with right-sided weakness and difficult speech with moderate confusion suggest left internal carotid artery insufficiency. Left hemianopic vision loss and left-sided weakness might imply posterior right hemisphere circulation deficit; that is, the right posterior cerebral artery. In the usual case, no headache is associated and syncope rarely is present. Duration of the deficit may be minutes to several hours. Recovery usually is complete. A presumptive diagnosis should be considered promptly when this type of history is present.

The neurological examination should give findings supporting the history. Such an examination may show bruits in the neck, vague paresis, subtle sensory changes, retinal arteriosclerosis, or the like. However, a neurological examination showing no abnormalities is common. A patient with persisting major neurological deficits is no longer in the reversible phase of cerebral vascular insufficiency. At least a small stroke is present. Prediction of exact reversibility is not reliable on the first examination. Frequently orthostatic hypotension can be shown to exist, usually transient when the patient stands up from a sitting or reclining position.

The complete workup is best done in the hospital once a presumptive diagnosis of reversible vascular insufficiency has been made. General, physical and neurological evaluation needs support by computed tomographic scan which distinguishes among infarction, hemorrhage, and no infarction—and on occasion may even show tumor. Complete cerebral angiography is mandatory

in most cases. This study is particularly important to identify clearly vascular insufficiency as the basis of complaint.

Angiography should show (1) the orifices of the four major cerebral vessels to brain from aorta (carotids and vertebrals), (2) the course of these vessels in the neck through the base of the skull and (3) the intracranial circulation to indicate the entire cerebral vasculature including possible collateralization vessels supplying the areas of suspected flow impairment.

Whereas angiography *may* show intimal plaques at the origin of the carotid or vertebral arteries with implied flow impaired, it also may show an unsuspected complete occlusion of an internal carotid artery. In either case, complete study of the collateral vessels supplying the "impaired area" is then advisable. The Circle of Willis is the major source of collateral supply to the areas of the brain dependent on the major cerebral arteries. This is very important in surgical considerations and must be shown clearly. In addition, angiography should show all arteries possibly involved in collateral supply. As an example, the ophthalmic artery may bypass an occluded internal carotid; a middle cerebral artery may provide "meningeal anastomosis" to the anterior cerebral, or the reverse.

Neurosurgical vascular operations are effective in alleviating episodic cerebral vascular insufficiency syndromes and in providing further recovery of lost central nervous system function in certain RIND syndromes. Carotid endarterectomy can relieve stenotic carotid artery flow effectively and excise sources of embolization. Neurosurgical evaluation for such operations includes thorough study of collateral supply to the part of the brain involved and, in most instances, studies of involved regional cerebral blood flow by isotope (Xenon) techniques, both before and after operation. This aids in establishing not only the diagnosis but also indicates the effectiveness of the operative procedure. A carotid plaque does not necessarily need to be removed. Careful correlation of symptoms, finding and flow studies now identify a need for this procedure much better than in the past. The operation is done by vascular surgeons and neurosurgeons, but the role of neurosurgeons now is clearly broad and very effective.

Microsurgical cerebral vascular anastomoses, as now carried out by neurosurgeons, anastomose extracranial vessels to intracranial vessels. Under high magnification, such anastomoses have gained stature for superficial temporal artery (in scalp) to middle cerebral artery anastomosis in cases of internal carotid or medial middle cerebral artery obstructions. Continued neurological improvement may continue for several months after such a procedure is carried out.

Problems of basilar artery insufficiency involving loss of a vertebral artery on one side may be greatly helped by neurosurgical microanastomosis of a high cervical-occipital vessel (extracranial) to the intracranial vertebral or posterior-inferior cerebellar artery on the opposite side. Such procedures have produced increased flow in the basilar artery with pronounced improvement in symptoms.

Neurosurgical management of stroke due to obliterative vascular disease requires early recognition of the syndrome, prompt and thorough workup, and effective, complete surgical treatment. The results of this approach are improving yearly.

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Neck, Head and Arm Pain

COMBINED HEAD, NECK, SHOULDER (often scapular) and brachial pain usually means involvement of mixed spinal nerves in the cervical region. Although the most common cause in adults is degenerating intervertebral disc disease, physicians must recognize that entrapment processes, congenital deformations, trauma, neoplasia and infectious processes may be prominent among other conditions that can be responsible for such a syndrome. This constellation of pain requires either (1) that there be primary irritation of posterior nerve roots (or mixed spinal nerves) to an extent that includes innervation of the posterior scalp and cervical regions plus the neural supply at least to the shoulder and brachium, or (2) that there be irritation of structures that derive their innervation from such a neural distribution whereby pain may be referred into the areas noted.

Direct nerve root participation in the syndrome usually is identified by the characteristics of pain of the nerve-root origin whatever it may be: (1)

perceived in the expected territory of the known anatomical distribution of the root, (2) aggravated by postures or maneuvers which physically encroach on the nerve root including the Valsalva maneuver and (3) relieved by measures which ease mechanical distortion of the neural tissue. Problems arise, however, in assessing disease when the indirect or referred-pain mechanisms are presumed to be operative in the absence of evidence of direct neural involvement. An example in point is the inadequately supported proposal that headache, as the dominant symptom, on occasion can be attributed to C5-6 or C6-7 intervertebral disc disease and effectively treated by such operative procedures as disc excision with or without interbody fusion.

When a comprehensive history and examination exhaust the other causes of direct and primary neural involvement leaving cervical disc disease as the remaining consideration to explain the pain syndrome, the diagnostic battery of neck manipulation, plain radiological study and contrast myelography are indicated. The precise identification of the offending disc may be substantially aided by the additional use of *analgesic* discography whereby surgical procedures may be avoided upon cervical interspaces which, while possibly diseased, are not responsible for the pain.

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Revolution in Neurodiagnosis: Computed Tomography of the Brain

COMPUTED TOMOGRAPHY (CT scan) of the brain has revolutionized neurodiagnosis as did ventriculography and pneumography in the 1920's, cerebral angiography in the 1940's and radioisotope brain scanning in the 1950's. Scanning technology is evolving rapidly to provide faster scans with finer resolution and display of the brain in coronal as well as horizontal slices. Except in showing vascular abnormalities (occlusive disease, aneurysm, arteriovenous anomaly, tumor blood supply) and lesions adjacent to the skull base (parasellar neoplasms), computed tomography has greatly diminished the use of pneumography, arteriography and radioisotope scanning. However, the occasionally false positive or negative CT scan demands that interpretation be expert and the scan be correlated with the clinical evaluation of a neuroclinician. The CT scan cannot replace the history and physical examination. In many cases the traditional neurodiagnostic studies will have to provide the diagnosis or supplement the CT scan.

The CT scan is a rapid, safe and noninvasive procedure except for uncooperative adults and children, in whom heavy sedation or general anesthesia may be required to control motion artifact. Large volume contrast enhancement risks allergic reactions.

The CT scan complements arteriography in the evaluation of the stroke syndrome since it accurately differentiates cerebral infarction and cerebral hemorrhage. However, in 20 percent of cerebral infarctions enhanced contrast occurs in the first week and they must be differentiated from a neoplasm. Hemorrhage in certain sites suggests aneurysmal bleeding and directs definitive arteriography.

The CT scan with contrast shows 95 percent of supratentorial and infratentorial neoplasms and shows tumor cysts and peritumoral edema. The scan also displays the number of metastatic cerebral lesions more accurately than other procedures. Postoperative tumor recurrence and the effectiveness of radiotherapy and chemotherapy can be ably evaluated by serial CT scans.

Earlier diagnosis of brain abscess is possible with the contrast enhanced CT scan. Serial scans follow the size of the abscess cavity and show the presence of daughter abscesses in need of drainage better than any other procedure.

The management of craniocerebral trauma is aided greatly by immediate serial CT scanning. The scan differentiates contusion and edema from intracerebral hematoma and displays the dynamic evolving pathological conditions of brain injury (multiple lesions, hematomas in the posterior fossa and frontal areas, delayed parenchymal hematomas, correctable postoperative complications) better than other diagnostic procedures. Occasionally, a subdural hematoma is isodense with brain tissue on CT scan and arteriography may be necessary to aid in the diagnosis.

The CT scan simplifies the evaluation in a neonate or infant with a large head and helps to select those patients in whom invasive diagnostic procedures are required. Serial scans display changes in ventricular size and aid in management decisions in the long-term care of hydrocephalus.

At the same time we accept the benefits of the CT scan, we must realize that uncontrolled requisitioning of the scan in the absence of clinical indications is an expensive abuse of a fine procedure.

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Treatment of Peripheral Nerve Injuries

TRAUMA TO A peripheral nerve may be by blunt force to the soft tissues, traction caused by dislocation or fracture of adjacent bone, or a compound wound with direct laceration. Correct diagnosis and management is based on analysis of the following features: (1) nature of injury, (2) status of nerve function distal to wound, (3) inspection of wound, (4) site of wound in relation to known anatomical positions of nerves and (5) severe injuries to soft tissues, tendons, bones or joints.

Unless there is progressing neurological deficit, treatment of blunt trauma is expectant and nonsurgical for four to eight weeks, with frequent neurological reevaluation and serial electromyography to determine the need for exploration and possibly neurolysis.

Primary suture of the divided nerve after a compound injury should be done only under ideal conditions; that is, (1) a cleanly lacerated nerve without crush or adjacent tissue damage, (2) minimal contamination, (3) approximation of nerve ends without stretching and without extending the incision, (4) repair within 24 hours of injury and (5) a competent and experienced surgeon using the latest techniques of nerve repair. Except in the rare situation presenting these favorable conditions, the nerve ends should be identified and tagged for subsequent fascicular orientation by sutures on matching anatomical positions of each nerve end. An overlapping stay suture of nonabsorbable material may be used to prevent retraction of the nerve ends. Secondary suture should then be done in three to six weeks, after associated injuries have resolved and satisfactory skin protection is present.

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The Warning Leak as a Clue to the Presence of an Intracranial Aneurysm

THE GENERALLY ACCEPTED statistic that a 50 percent mortality is associated with the initial rupture of an intracranial aneurysm contributes to the nihilistic approach to this condition by many physicians. It is important to recognize that this need not be the case, however, as evidenced by recent reports that many patients who suffer a devastating subarachnoid hemorrhage have experienced a mild or "warning" leak in the weeks preceding the major ictus which has gone unrecognized by their physician. One can only speculate that had the "warning leak" been investigated thoroughly the aneurysm might have been repaired and there might have been a much more favorable outcome.

The most important adjunct to recognizing a "warning leak" is to be aware that they do occur. However, a brief review of the subject may offer additional assistance to the busy physician confronting a patient with the all too frequent complaint of headache. Unfortunately, headache is the only symptom of "warning leak" because there is no associated neurologic deficit. There is nothing specific about the headache of a "warning leak" to separate it from other causes of head pain, so the differentiation must be made on the basis of the individual circumstances. The best first step is to exclude the common headache syndrome.

- *Migraine headache.* Migraine headache is a specific syndrome which is usually very familiar to a migraine sufferer because he or she has had it for many years. It begins on one side of the head, is throbbing in character and is relieved by administration of a mixture of ergotamine tartrate and caffeine (Cafergot®).
- *Tension headache.* Most people with tension headache have a headache pattern with slow buildup suboccipitally. They also usually have a long history of headache and are not sufficiently incapacitated that they cannot continue to function.
- *Sinus headache.* Sinus headache is usually associated with fever, nasal discharge and tenderness over the involved sinus. Most people with sinus headache have a history of previous episodes in the past.
- *Cluster headache.* Cluster headache is almost always associated with pain about the eye and tearing, conjunctival erythema or nasal stuffiness.

As the name implies, episodes of head pain come in clusters and the patient usually has experienced it before.

From this very brief review it should be obvious that the most important diagnostic criterion for a warning leak is that it is a new type of headache for the patient under consideration. In addition, the "warning leak" headache is sudden in onset, not associated with fever and does not respond to mild headache remedies. Therefore, to insure proper diagnosis any patient over 40 years old in whom a headache of abrupt onset develops which is atypical for him or her and persists for 24 hours should be considered for the possibility of a warning leak.

The only way to rule in or out a small subarachnoid hemorrhage is to do a lumbar puncture, but this does not exclude an unruptured aneurysm. The potential advantage of establishing the diagnosis early in the course of the disease is sufficient to justify an aggressive approach. If the lumbar puncture is done with a 20 gauge needle it can be carried out on an out-patient basis with the patient returning home after a 30 minute rest if the tap is negative. If the tap is positive a cerebral arteriogram is, of course, in order.

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Transnasal Approach to Pituitary Tumors

THE SUBLABIAL-TRANSNASAL-TRANSSPHENOIDAL removal of pituitary tumors has been revived as a direct result of two technical advances: (1) the operating microscope with its intense illumination and magnification both being required for extirpation of 3 to 5 mm adenomas buried within traoperative fluoroscopic visualization of the sur- an otherwise normal pituitary gland, and (2) ingical field.

Most large nonsecreting pituitary tumors (for example, the classical "chromophobe" adenoma causing a ballooned sella, hypopituitarism and bitemporal hemianopsia) can be removed safely and effectively by the transsphenoidal approach as an alternative to craniotomy. In addition, the transsphenoidal technique has ushered in a fascinating new field of endocrine microsurgery. Secreting pituitary microadenomas measuring 2 to 10 mm in diameter can produce distinctive manifestations of hormone overproduction: gigantism and acromegaly (growth hormone), Cushing disease (adrenocorticotropic hormone) and the Forbes-Albright syndrome of amenorrhea and galactorrhea (prolactin).

The clinical features evolve in advance of changes detectable on standard radiographs of the skull, but sella turcica polytomograms will show subtle abnormalities in most cases. Practically speaking, the diagnosis of a secreting pituitary microadenoma is based upon endocrine criteria. The surgeon's dual objective, complete removal of the microadenoma and preservation of normal pituitary function, has been achieved by transsphenoidal microsurgery with results equal or superior to those obtained by other surgical and nonsurgical methods.

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Percutaneous Radiofrequency Cervical Cordotomy: Treatment of Chronic Intractable Pain

PERCUTANEOUS RADIOFREQUENCY CERVICAL CORDOTOMY is a procedure with stereotactic features made possible by recent advances in radiographic technology. Under local anesthesia, a needle electrode is inserted percutaneously into the spinothalamic tract of the cervical spinal cord. Needle placement is monitored by x-ray control and impedance measurements. Precise localization is verified by stimulation. A radiofrequency current is used to make a thermal lesion, the size of which is a variable of electrical amperage and the time applied. Lesion making is monitored clinically by patient response. Barring concurrent medical problems, most patients are ambulatory on the following day and are able to leave the hospital within two or three days.

Satisfactory results depend on appropriate patient selection based upon explicit criteria. The pain should be chronic and intractable—that is, nonresponsive to disease specific therapy. Significant emotional problems must be properly evaluated and screened. The procedure usually is limited to patients with malignant disease. However, in selected cases, it may be of benefit for patients with benign disorders.

Assurance of a well-controlled and precisely placed intraspinal lesion makes this procedure effective and reasonably safe. Pain as high as the upper cervical area is amenable to treatment. Since general anesthesia, open surgical procedures and prolonged recuperation are avoided, it is well tolerated, even by chronically ill and debilitated patients. In the event that pain eventually recurs, the procedure can easily be repeated.

Percutaneous radiofrequency cervical cordotomy significantly augments the neurosurgical therapeutic armamentarium by extending the indications and applications of surgical treatment of pain. It merits consideration when drug therapy, electroneurostimulation, alternative ablative neurosurgery and behavioral modification therapy are ineffective or inappropriate, and can be optimum treatment in pain syndromes of malignant origin.

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Rheumatoid Arthritis Quadriplegia

IN THE PAST FEW YEARS increasing attention has been focused on the complications of rheumatoid arthritis. It has become clear that not only is the cervical spine frequently involved in this disease, but that atlantoaxial subluxation is relatively common. Atlantoaxial subluxation may not only cause severe symptoms, it may threaten the integrity of the spinal cord and lead to quadriplegia or sudden death. It is, therefore, incumbent on physicians to recognize this complication and treat it.

Common signs and symptoms of spinal cord compression are difficult to evaluate because of joint and muscular changes. Hand paresthesias, weakness in one or both lower extremities, mild weakness of hip flexors to severe quadriplegia can occur. Reflex changes and sensory alterations are helpful.

Radiological studies, including lateral views of the cervical spine in extension and flexion, tomography and cinefluorography will show the forward subluxation of the atlas, producing compromise of the neural canal. Myelography is rarely needed.

Conservative management consists of the use of a cervical collar or brace to lessen spinal cord trauma.

Fusion to immobilize the subluxing segments of the occipital cervical junction can be done by wiring the two upper cervical segments and fusing with iliac bone. Satisfactory decompression of the spinal cord and an arrest of progressive neurological changes can be accomplished.

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Percutaneous Thermocoagulation of the Trigeminal Ganglion

FACIAL PAIN of paroxysmal trigeminal neuralgia or tic douloureux is an intractable and disabling affliction. Current treatment follows a consecutive regimen beginning with medical management using such drugs as diphenylhydantoin (Dilantin®) and carbamazepine (Tegretol®). In the event drugs are ineffective, nerve blocks and avulsions usually are attempted. If pain recurs, operative procedures may be carried out on the trigeminal nerve, ganglion or tract through the customary subtemporal or suboccipital approach.

Percutaneous thermocoagulation of the trigeminal ganglion represents a new and effective surgical approach to the trigeminal nerve in the treatment of trigeminal neuralgia and, to a lesser extent, facial pain of other causes. Although popular in Europe several decades ago, the procedure was abandoned because of an unacceptably high morbidity and mortality. Refinements in technique made possible through advances in radiology and electronic bioengineering have assured its acceptance in this country.

The procedure is done under local anesthesia, which is usually supplemented by the intravenous administration of a short-acting barbiturate (Brevital®). Under x-ray monitoring, a needle electrode is introduced percutaneously into the gasserian ganglion through the foramen ovale. The electrode can be placed selectively into any of the three divisions depending upon the distribution of pain. Final electrode placement is verified by stimulation. A radiofrequency generator is used to make a thermal lesion, the size of which is a variable of power output and time. Lesion making is monitored by a thermistor. Through selective coagulation, pain relief can be achieved by producing marked hypalgesia in the affected division avoid-

ing total anesthesia and loss of the corneal reflex.

This procedure is effective and reasonably safe, making it acceptable to both patients and physicians. By eliminating the stresses and dangers of a general anesthetic, an open operative procedure and a prolonged period of recuperation, the procedure is well tolerated even by elderly and debilitated patients. In the event pain recurs it can readily be repeated. Percutaneous thermocoagulation of the trigeminal ganglion represents a reasonable alternative to the surgical treatment of facial pain and rapidly is becoming the treatment of choice for trigeminal neuralgia after the failure of medical management.

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Intracerebral Hematoma

HEMORRHAGE WITHIN BRAIN SUBSTANCE is a common cause of major neurologic disability and death. It may occur under many circumstances, but is most commonly seen in hypertensive patients of both sexes, usually occurring during periods of activity and producing neurologic symptoms and signs over a short time-interval, sometimes within minutes and usually within 24 hours. Unlike subarachnoid hemorrhage, secondary to aneurysms, the hemorrhage does not tend to recur. Brain tissue may be destroyed, but often is compressed and displaced. With the advent of computed tomographic scanning, lumbar puncture usually is not necessary. Severe headache is a very common, but not invariable, accompaniment of the development of intracerebral hematoma.

The probable presence of hematoma within the brain may be established on clinical grounds in most cases, and may be confirmed by the finding of an avascular mass on angiography. Computerized axial tomography will accurately identify the presence, size, configuration and location of an intracerebral hematoma, or identify a coexisting primary vascular lesion. Possibly of greatest importance is that the neurological deficits produced by an intracerebral hematoma may be reversed by surgical removal of the mass, with relief of brain compression and often a dramatic return of the neurologic status toward normal. The combination of the availability of recent, accurate and safe diagnostic and surgical techniques, including brilliant illumination and direct visualization afforded by the operating microscope following removal of the hematoma, justifies an active and energetic approach to every patient in whom the presence of intracerebral hematoma is suspected.

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Penetrating Brain Injury

BRAIN TRAUMA secondary to intracranial passage of a bullet or other object is one of the most serious categories of central nervous system injury. However, a commonly held belief that all such trauma is uniformly fatal is unfounded. There are several reasons for optimism following prompt, aggressive surgical treatment in selected cases, as extensively documented in both military and civil experience.

First, the site of brain injury may be superficial, or confined to "silent" or less critical areas such as frontal or temporal tip. Second, the site of skull penetration, with frequently associated complex fracture, may provide immediate decompression and relief, or control in part, of rising intracranial pressure. It may be for this reason that every neurosurgeon has seen cases of loss of some brain tissue through the skull aperture with later recovery. Third, the missile tract itself may be slender and the elevated pressure and neurologic findings may be the result of the presence of hematoma, within or adjacent to the tract. Such hematoma may be extruded from tract during exploration, and removal often is followed by restoration of normal intracranial pressure. The improvement in neurologic status is sometimes immediate and striking.

Passage through the brain of high velocity missiles may be expected to produce more widespread cerebral injury. A complication of both low and high velocity trauma is the later development of cerebral abscess, if debridement with removal of bone fragments has been incomplete. In all cases, x-ray studies of the skull are required to show the extent of bony injury, the position, when present, of in-driven bone fragments, and the precise trajectory involved. Both angiography

and computed tomography may provide information concerning the location of hematoma, ventricular status and vascular injury. When obtundation, coma, or motor or other findings are the result of pressure effects secondary to hematoma, exploration in even profoundly unconscious patients, in selected circumstances, may be rewarding.

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Cauda Equina Claudication Syndrome

ARTERIAL INSUFFICIENCY secondary to severe vascular disease is an established cause of intermittent limping, which is the meaning of the term "claudication." In recent years postural and ischemic neurogenic claudication mechanisms which lead to pain, sensory changes and weakness in some patients with a narrow lumbar spinal canal have been described. This neurogenic intermittent claudication syndrome usually occurs in older men, and is characterized in part by the onset, with exercise, of a specific pattern of numbness, tingling or dyesthetic sensation in buttocks and lower extremities, accompanied, if exercise continues, by weakness which may prevent further walking. Pain is not invariable. Frequently, the patient chooses to maintain a position of flexion of the lumbar spine during standing, walking or sleeping. Symptoms are produced by an erect posture and are gradually relieved by sitting or flexing the spine. Findings on neurological examination may be, and often are, normal, except for a nonspecific decrease or absence of ankle reflexes, which is of little diagnostic value in older patients. Other reflex, motor or sensory findings may be present only during activity. Except in those patients with coexistent serious vascular disease, the pulses are normal, and there are no trophic changes. Lumbar spine x-rays may suggest the presence of a narrow lumbar spinal canal. Arteriograms, when obtained because symptoms are thought to be secondary to vascular disease, may show no abnormalities. In contrast, myelography shows severe or complete spinal block, and cerebrospinal fluid protein values often are increased. Usually lumbar puncture is difficult in such patients and proper positioning of the needle may require fluoroscopic control and cisternal puncture may be necessary.

When the patient's symptoms are the result of a narrow spinal canal producing cauda equina compression, wide laminectomy throughout the stenotic areas will very often be followed by complete relief of symptoms and return to normal, unrestricted activity. Pronounced improvement frequently has been noted even in cases with profound preoperative symptomatic disability.

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EDITORIALS

Patient's Access to Physician's Records

THE COMPLEX ISSUE of a patient's right to access to his or her own medical record is receiving more and more attention. Many physicians still in practice can remember when a physician's office records were personal and privileged, and contained such information as the doctor thought he needed to help in the care of the patient. Similarly the hospital records contained the information necessary for the proper care of the patient while in hospital. Both kinds of records were considered confidential, privileged and not to be revealed since the ailment was held to be the business of the patient and no one else. The tradition of this kind of confidentiality, and recognition of the need for it, extends back to the time of Hippocrates and no doubt further. But nowadays a variety of third parties have an increasing interest in what is wrong with a patient and what was done about it, and patients themselves are seeking access to their medical records no doubt for a number of reasons.

The trend of the times is clearly toward greater freedom of information generally, and more ready access to information about oneself—particularly that which may be recorded accurately or inaccurately in the automated information storage systems of governmental and nongovernmental agencies. In this context freedom of access to information recorded about oneself is clearly a good thing. But the human experience, back to 400 BC and beyond, suggests that there may be times when it may not be in a patient's best interest, or in the best interest of others, for anyone but the physician to be aware of certain kinds of information or certain unproven suspicions or concerns that physicians may have appropriately entered into their personal medical record for the patient. For example, every experienced practicing physician has seen patients with unexplained and undue anxiety about their condition until it is discovered that they have misinterpreted or misunderstood something they overheard, or read about—perhaps in their own hospital chart, which happens sometimes. The jargon of medicine can be frightening to patients unless it is fully understood. Terms such as "complete heart block" and "paroxysmal auricular fibrillation" can be very threatening to a patient with heart trouble unless they are carefully explained.

At times revelation of information in a medical record may be more directly detrimental to a patient's health. As an example, something in the record may indicate there is little hope for the patient. This can be a cruel and even shattering realization for many persons. When this has happened, experienced practicing physicians have seen patients give up, throw in the sponge so to speak, or go into a profound depression or even commit suicide—hardly the aim of therapy, and in ordinary judgment not the best thing for the patient. These outcomes are particularly tragic when there might have been a number of happy, useful and even productive years ahead for the patient with appropriate treatment and management. Another situation where the privacy of a medical record should be protected is when there is information that would unnecessarily harm others than the patient, such as the effect upon a happy family if they were to find in the medical record of a recently deceased and revered father that he in fact had an active homosexual life on the side, with more than occasional bouts of venereal disease contracted in this fashion and requiring medical diagnosis and treatment.

One might also ask why a patient would want to see his or her medical record anyway. There might be a genuine uncertainty about what the

situation is, what is wrong and what is being done about it. This might easily be conceivable in a complex situation where a number of physicians are involved and no one of them has really communicated with the patient. This could be an understandable and valid reason for a patient to want to examine the medical record. A second and more likely reason might be a kind of morbid curiosity on the part of a patient. There are such patients, and they are the ones likely to misunderstand or misinterpret what they read, often looking things up in a library, and they are prone to develop additional and unnecessary anxieties as a result—and may begin to treat themselves unbeknownst to the physician who is attending them. Or a patient may be trying to check up on the doctor and pass judgment on the treatment. Here the question becomes to what extent is it in the interest of a patient to act as his or her own physician. It is said, and with some reason, that a physician who acts as his own doctor has a fool for a doctor. It is hard to conceive that this role is likely to be in the best interest of a relatively uninformed patient. And yet another, and in these days even more likely, reason for a patient to wish to peruse his medical record is dissatisfaction with the physician which may lead to intent to sue. This is a quite recent phenomenon and has introduced a new purpose for the physician's records. It is now an instrument for the protection of the physician as well as his instrument to help him serve patients.

If things continue as they are it is likely that we shall have "open season" on medical records. The confidentiality of the hospital record has already been pretty thoroughly eroded and a physician's personal office records can now be subpoenaed. It is likely that this is only the beginning. As the trend continues physicians will understandably take greater protective measures and develop alternative means of maintaining the information they need to properly care for their patients and the medical record will be maintained strictly "for the record," including for purposes of the physician's legal defense. Privileged information will be communicated by telephone or other means much as is now done in other situations where consumers have access to records that were previously considered confidential. All of this will add yet another increment to the cost of medical care, and like so many of the new legal and regulatory requirements now imposed upon medicine and the health care system, the added cost will add little if anything to patient satisfaction or to better care. The extra cost for a "benefit" which may actually be harmful to many will be passed on to patients and third party payors, including government. It seems unlikely that much of anything will be gained by anyone, yet this no doubt is what will be done.

—MSMW

Lead Is Where You Find It

To paraphrase a song, "Lead is where you find it/Don't be blinded/It's all around you/Everywhere." Everywhere, indeed; even in Los Angeles. And do not be blinded by an inability to define its threshold of toxicity. The article by Wesolowski and associates in this issue illustrates these two important points—the locale of the lead problem among children and the level of blood lead that is unacceptable are different from what we thought them to be 15 years ago.

Symptomatic childhood lead poisoning in the United States was generally viewed as a health problem limited to the urban, northeastern cities with their blighted housing, although midwestern cities contributed a fair share to the literature on lead poisoning. Beginning in the early 1970's screening programs were conducted in rural areas and small towns. Elevated blood lead levels were found in children from these presumed pristine sanctuaries. In 1973 the Center for Disease Control initiated a Childhood Lead Based Paint Poisoning Prevention Program that funded projects for lead screening of children in all regions of the United States. The California project was one among 77 conducted in 1975, during which time 440,650 children were screened.[1] Children with elevated lead levels were found in communities from Augusta, Maine, to Los Angeles. Nationally, 6.5 percent of all the children tested had elevated blood lead levels confirmed by repeat testing. The data represented populations of young children, selected for their residence in older, deteriorating housing, as was the case in the California project.

Criteria for screening based on the age and condition of housing are reasonable because the major source of lead in symptomatic lead poison-

ing has been peeling, lead-laden paint. Pica was the modus operandi. Other known sources leading to lead encephalopathy have been burning lead batteries and fruit juice stored in improperly glazed earthenware containers. As the interest in lead poisoning expanded from diagnosis and treatment of children with symptoms to identifying asymptomatic children with elevated blood lead levels, other exposures to lead have been recognized. The fallout from automobile exhaust and industrial pollution produces lead-laden dust in homes and schools.[2] Lead smelters fill the surrounding atmosphere with high concentrations of lead. Even efforts to remove lead from walls and woodwork may inadvertently produce lead-laden fumes or spread pulverized fragments that are difficult to remove. Pica, then, is not necessary for increased ingestion of lead. Breathing the contaminated air near a smelter or innocent hand-to-mouth activity with hands coated with contaminated dirt and dust becomes a means of increasing a child's lead intake.[3]

Lead poisoning was initially approached as a clinical entity. Patients had the exposure and symptoms, and the diagnosis was confirmed by anemia, radiographic appearance of the long bones or coproporphyrinuria. The determination of a blood lead level was not often carried out. In the 1960's atomic absorption spectroscopy facilitated the measurement of lead on large numbers of blood samples. The improved technology plus the increased interest in detecting lead poisoning before symptoms developed led to large scale screening programs. The first was conducted in Chicago in 1966. Screening programs depended on the blood lead level as the essential criterion for diagnosis and management. For the Chicago program the cutoff value was 50 μg per 100 ml whole blood. Four years later the Surgeon General of the United States recommended that 40 μg per 100 ml be used as evidence of undue absorption of lead. The upper limit of normal for blood lead according to the Childhood Lead Poisoning Prevention Program is 29 μg per 100 ml.

For years children with blood lead levels in the 30 to 50 μg per 100 ml range were largely ignored. They make up the largest percentage of children who are detected by screening programs. What happened to those children whose lead levels were not high enough to warrant careful surveillance when our standards, ironically, were "too high"? What should be our response now?

The consequences of slight elevations of blood lead levels in children are difficult to ascertain and the difficulty has led to the lexicon used in describing the lead problem. There is *undue absorption of lead*—the statement rightly implying that some absorption is everyone's due. An *increased body burden of lead* is not as bad as *classical lead poisoning*. The terms *subclinical* and *asymptomatic lead poisoning* lead one to question what is actually meant by poisoning. The confusion in establishing criteria and the resort to ambivalent lexicology are due, in part, to careless mixing of indices of absorption or exposure and indices of toxicity. It is well to keep in mind what the various tests mean.

The concentration of lead in the blood is an index of absorption. Repeat testing may show variation between the two samples and in the California project 40 percent of second samplings had a lower lead concentration. Technologic factors may be partly responsible, but it is also important to realize that a blood lead level reflects a single point in the complex kinetics of exchange of lead between red cells and tissue.[4] One can interpret the blood lead level in two ways.

First, it can be used solely as evidence of increased absorption of lead, after one has established the upper limit of normal. In so doing, no effort is made to define what the toxic level is. Therefore, the data of Wesolowski and co-workers indicate that less than half of the children tested had a lead level commensurate with normal exposure (the percentage might have been greater if repeat sampling had been done in all cases).

Another interpretation of the blood lead level relates the value to some index of toxicity, realizing that the lead level itself is not a measure of toxicity. This is far more difficult because the correlation between toxicity and lead level is not always precise and, furthermore, the critical index of toxicity is very difficult to establish.

The sensitivity of the heme synthetic pathway has made measurement of its enzymes and substrates a means of assessing metabolic toxicity. Currently, erythrocyte protoporphyrin (EP) is the most frequently measured metabolite in evaluating children for lead poisoning. Elevation of EP is also a useful test for iron deficiency in children. It is not surprising that in screening children at risk for both lead poisoning and iron deficiency, there will be instances of normal lead level and elevated EP. Such a discrepancy could also occur if sampling were done at the time of an ebb in the fluctuation of blood lead. The EP level is not subject to

wide daily variations, since the concentration within the red cell is constant for the cell's 120-day life span. Although the Center for Disease Control guidelines considered an EP value of less than 60 μg per 100 ml of whole blood as normal, studies indicate that the upper limit of normal in children is closer to 45 μg per 100 ml of whole blood.[5] So the group of children with blood lead levels between 30 and 50 μg per 100 ml and EP values less than 60 μg per 100 ml should not be ignored.

In general, projects such as the one in California, will find that most of the children with elevated lead levels and EP values are asymptomatic and the elevations are not pronounced. How to relate the blood level or EP value to the risk of clinical toxicity is the dilemma of assigning a threshold of toxicity. Certainly it is the neuron, rather than the red cell precursor with deranged heme synthesis, that is the chief concern. The manifestation of neurologic damage in asymptomatic children will not be apparent for some years after the period of increased ingestion and is likely to consist of learning or behavioral disturbances. In the most relevant, though not a perfect study, de la Burde and co-workers found that poor academic performance, primarily due to behavioral problems, was more frequent among children with increased exposure to lead during early childhood.[6]

The lead problem in children is a frustrating one. The full impact is not known. Safe elevations cannot be confidently given. Successful management depends on socioeconomic and cultural factors as well as medical practice. Each community must consider whether there is a population of children at risk. Then a screening program must find them. The legacy of old, substandard housing and the likelihood of continued pollution will make lead a problem for a long time.

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PSRO — Update 1977

THIS IS THE FOURTH in a series of more-or-less annual editorial reports on Professional Standards Review Organization (PSRO) developments. One senses that during the past year slow but steady progress has been made toward implementing the complex and potentially very important PSRO law. It is expected that by the end of this federal fiscal year (30 September 1977) there will be 119 conditional PSRO's in place and 70 planning PSRO's proceeding toward conditional status, with only a few of the designated areas remaining unfunded. In a very few areas no PSRO has yet developed. The present law has extended the time professional organizations will have priority in establishing PSRO's until 1 January 1978. The hope has been expressed by the government that it will not be necessary to invoke the alternative means provided by the law to create PSRO's in those areas which have not been able to establish one.

Much more remains to be resolved at the federal level. The tension between the law's dual priorities of cost control and quality assurance continues, with neither having gained a clear ascendency within the federal bureaucracy. This is probably as it ought to be. Too much emphasis on one adversely affects the other. Attempts are underway at the bureaucratic and legislative levels to clarify the relationships of PSRO's to the state review mechanisms for Medicaid programs and to the federally mandated medical review boards of the national End Stage Renal Disease (ESRD) program. The confidentiality issue also has not been settled. The Privacy Protection Study Commission, created by Congress in 1974, has called upon the Department of Health, Education, and Welfare to require hospitals to adopt procedures to guard the privacy of medical records as a condition of qualifying for Medicare and Medicaid reimbursement. But what actually will be done to protect the privacy of physicians and their patients remains to be seen. Meanwhile there is talk of developing patient, physician and institutional profiles for analysis to make comparisons

of patterns of care by similar practitioners and institutions for similar patients, and so to identify exceptional patterns which will allow PSRO's and hospitals to use their resources in the most efficient ways.

All of this appears to be by way of preparation for National Health Insurance which is envisioned as requiring effective mechanisms of quality and cost control. It is noteworthy, and significant, that of all the control mechanisms being tried by government, the PSRO mechanism emerges as the only one clearly accountable to the medical profession. In times such as these, this should be a powerful incentive to physicians to make PSRO's work and work well in the best interests of all concerned.

—MSMW

Rheumatoid Synovium

Its Proliferation, Heterogeneity and Polarization

All of the changes observed suggest that a viral agent may form the basis for these alterations [in rheumatoid synovium]. However, studies to date have failed to isolate or identify the putative causative virus and the search continues.

THESE SENTENCES end the opening abstract in the lucid review of the biology of the rheumatoid synovial membrane by Haselwood and Castles published in this issue. It is a good review and an accurate summary. The truth may be that a virus is involved initially, but that its role in producing the proliferative and destructive lesion of rheumatoid arthritis may be minimal. It may even be true that virus infection may be (as is one of the possibilities in multiple-choice examinations) "true, true and not related." If a virus is found not to be clearly *the* cause of rheumatoid arthritis, it may not be the inadequacy of our laboratory techniques so much as it is the erroneous assumption forming the basis of our approach to most diseases in this day and time—that is, the assumption that if we search hard enough, a single metabolic (often genetic) defect or underlying infectious agent capable of replication and derived from our environment eventually will be identified as the initiating factor of each ailment listed in our textbooks of medicine.

Common to all rheumatoid synovial tissues is a striking degree of nonmalignant proliferation, cellular heterogeneity and polarization. Every physician should take the opportunity to go into the operating room and observe an orthopaedic colleague carry out a synovectomy and compare the mass of brown-red tissue removed with the paper-thin transparent membrane which forms the "synovial membrane" of normal joints. Weight of the pathologic tissue may exceed that of the normal by 500-fold and have a similarly increased synthetic and degradative capacity as well.

The morphologic heterogeneity of the rheumatoid synovial lesion is most clearly evident by looking at thin sections by high resolution transmission phase microscopy.[1] Almost every cell has a morphology different from its neighbor. Multinuclear cells, lymphocytes, the other plasma cells and endothelial cells are most easily recognized. The majority of cells are distinguished by variegate shape, much cytoplasm and location amidst a low-density matrix of collagen fibrils and ground substance. Observation of the pannus/cartilage junction[2-4] shows that some of these cells have multiple thin cytoplasmic extensions penetrating cartilage matrix, and some have dense accumulations of rough endoplasmic reticulum. But because of the enormous numbers of these cells, who is to say that the apparent synovial "A" cells are not, instead, marrow-derived macrophages, or that both types of cell are not, in fact, synovial cells altered beyond functional recognition by lymphokines, connective tissue activating peptides or as yet unidentified humoral substances associated with the rheumatoid process? Dayer and co-workers[5] and Werb and associates,[6] using methods for study of function of dissociated adherent rheumatoid cells in culture, have focused interest on a dendritic or stellate cell with long, spiny cell processes extending radially from the nuclear area. This cell, which has morphologic characteristics similar to adherent cells of mouse spleen studied by Steinman and Cohn,[7] is present along with cells appearing as fibroblasts and with round cells (? macrophages) in these cultures. Interestingly, the number of dendritic cells in proportion to other cells in culture is often increased in cultures that synthesize and release large amounts of collagenase and prostaglandins. The argument for studying dissociated, adherent

cells of rheumatoid synovium, a procedure which enables one to examine the *function* of the cells within a few days of their removal from the patient, is that they may more accurately reflect the *in vivo* state than by studying fibroblast-like cells which have grown slowly out from explants of rheumatoid synovium. Cultures of the adherent dissociated cells have been shown to produce up to 100-fold more protease and collagenase than do similar numbers of cells passaged from primary cultures.[5] It seems probable that these and other functions of rheumatoid cells are mediated by their interaction with other types of cells in the lesion, and that the rheumatoid lesion cannot be understood without taking into account its pronounced heterogeneity, Dayer and associates have already shown that a factor produced by cultures of lymphocyte/monocytes can stimulate cultures of adherent rheumatoid synovial cells to produce increased amounts of collagenase and prostaglandins.[8] Newcombe and co-workers[9] have shown that cultured synovial cells exposed to prostaglandins become refractory or "desensitized" (as regards to cyclic AMP [adenosine 3′,5′-monophosphate] production) to prostaglandins or other agents. These investigators suggest that the chronic refractory state in rheumatoid synovium leads to an altered, potentially destructive pattern of metabolism in synovial tissue. Although it is somewhat neat, tidy and satisfying to think of the immunologic events in synovium as principal directors of stimulation and perpetuation of the proliferative lesion in rheumatoid arthritis, there must be other factors involved. In hemophilic arthropathy, for example, often there are synovial proliferation and joint destruction equal to that of severe rheumatoid arthritis, and adherent synovial cells in culture produce abundant quantities of destructive enzymes,[10] but a significant immunologic response in hemophilic synovial tissue has not been described.

The third characteristic, that of *polarization* of the rheumatoid lesion, is very difficult to study. Why doesn't the invasive process move centrifugally to invade skin or down along bones into muscle? Instead, it appears to have an avidity for the articular cartilage, subchondral bone and tendons within sheaths. Is it simply because these are moving parts? Or does a key lie in understanding the pathobiology of neovascularization by small capillaries? An inhibitory factor similar (if not identical) to the proteinase inhibitor of Kuettner and co-workers[11] has been isolated from articular cartilage which inhibits tumor-induced neovascularization.[12] Depletion of this by proteinases from polymorphonuclear leukocytes in synovial fluid or by similar enzymes from synovium itself may upset a sensitive balance resulting in neovascularization with subsequent destruction of cartilage. It is the vascular supply to the rheumatoid pannus that sustains its viability and destructive capacity.

The proliferative, heterogeneous and polarized lesion affecting moving parts constitutes the destructive lesion of rheumatoid arthritis. Its pathogenesis is probably multifactorial and linked inextricably to the immune response. We must continue, as with a jigsaw puzzle, to work upon it piece by piece.

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CASE REPORTS

Refer to: Reuler JB, Jones SR, Girard DE: Hypothermia in the erythroderma syndrome. West J Med 127:243-244, Sep 1977

Hypothermia in the Erythroderma Syndrome

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EXFOLIATIVE DERMATITIS is a syndrome with multiple causes, which include psoriasis, eczema, malignancy and drug reactions. There is, in addition, an idiopathic form.[1] It is characterized by generalized erythema, followed by profuse scaling, varying degrees of hair loss and nail dystrophia.[2] The systemic effects of this entity include high output congestive heart failure, enteropathy, gynecomastia, hyperuricemia, elevated basal metabolic rate and thermoregulatory disturbances.[3-7] We recently cared for a patient who died from hypothermia as a complication of generalized psoriasis. We present this case to illustrate this little appreciated association and to discuss probable pathophysiologic mechanisms.

Report of a Case

An 88-year-old white man was admitted to hospital for progressive weakness and confusion. The patient had been in excellent health all of his life save for psoriasis which was diagnosed about six months before admission and for which he was given a topical steroid cream. However, he was subsequently lost to follow-up by his private dermatologist. The family had noted that for the month preceding admission the patient had complained of being cold and was often found sitting in front of the fireplace despite room temperatures in excess of 75°F. During this time the patient also had severe scaling from his skin disease, and the family observed that there were piles of scales scattered over the floor of the apartment. For the two weeks before admission the patient complained of weakness, to the point of being bedridden, and evidenced mild confusion. There was no history of ethanol or other drug consumption, fever, change in voice or weight loss.

The patient appeared well nourished. He was oriented but lethargic. The rectal temperature was less than 32.2°C (90°F; below the scale of available thermometers), pulse was 40 beats per minute and regular and blood pressure was 110/60 mm of mercury without orthostatic change. The skin was cool with erythematous scaling lesions covering the chest, abdomen, back and all extremities—approximately 90 percent of the surface area. There were numerous superficial ulcerated areas and grayish, scaling plaques, most prominent on the lower extremities. There were no focal neurological findings. The reflexes were normal without delayed relaxation time. The thyroid was not palpable and there was no evidence of head trauma. Laboratory studies gave the following values: serum sodium, 153 mEq per liter; potassium, 7.3 mEq per liter; chloride, 120 mEq per liter; bicarbonate, 23 mEq per liter; glucose, 87 mg per 100 ml; blood urea nitrogen, 42 mg per 100 ml; hematocrit, 44 percent; leukocyte count, 8,800 cells per cu mm with normal differential; and platelet count, 55,000. Except for decreased platelets, findings on peripheral smear and coagulation studies were normal. Analysis of urine showed no abnormalities. Electrocardiogram showed sinus bradycardia with J-point changes characteristic of hypothermia.[8] On an x-ray study of the chest bilateral lower lobe infiltrates were seen. Neither blood cultures nor thyroid function tests were obtained.

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Initial management included warm peritoneal dialysis, with the temperature rising to 36.1°C (97°F) but falling again with its temporary discontinuation. The course was complicated by multiple cardiac arrests, pulmonary aspiration and hypotension. The patient expired on the second hospital day. On postmortem examination evidence was noted of a fresh myocardial infarction and aspiration pneumonia. A biopsy study of the skin showed elongation of the rete ridges with conspicuous vessels in the spaces between the ridges and hyperparakeratosis, all compatible with psoriasis. The hypothalamus, thyroid, adrenal and pituitary glands were normal.

Discussion

Hypothermia in association with exfoliative dermatitis was first described in 1952 by Mali, who reported elevated skin temperature measurements and poor thermoregulation when compared with normal subjects.[9] Several other reports have documented this phenomenon,[3-7,10-12] including the description of one woman with generalized psoriasis and a core temperature of 26.7°C (81.7°F).[13]

The mechanisms leading to deranged thermoregulation in exfoliative dermatitis are complex. Increased total skin blood flow coupled with a sharp increase in transepidermal water loss lead to increased heat loss by radiation, conduction and evaporation.[5,14] The ability to vasoconstrict in response to cold is decreased and, because of increased skin blood flow and temperature, cutaneous cold receptors are not activated, thereby abolishing a stimulus to shiver.[4] Conversely, exfoliative dermatitis may also be complicated by hyperthermia due to an increase in the basal metabolic rate, hypohydrosis and even increased heat absorption (such as after a warm bath) due to increased cutaneous blood flow. This may manifest itself in rapid development of hyperthermia in a patient with exfoliative dermatitis initially treated for hypothermia. It is possible that the unexplained high mortality in early reports of erythrodermas may have been the result of these hemodynamic and thermoregulatory problems.[15]

Several practical points in relation to these thermoregulatory derangements and patient care are noteworthy. Hypothermia may develop rapidly and the clinical diagnosis may be made difficult by confusing signs: lack of vasconstriction, increased skin blood flow and temperature, and lack of shivering. For these reasons monitoring of core temperature with a thermometer calibrated to lower temperatures is mandatory. Further, these thermoregulatory problems may obscure an underlying infectious process ("concealed pyrexia").[6] This comes about when the hypothalamic set point is elevated due to a true febrile illness[16] in a patient who is unable to vasconconstrict and has continued heat loss, with a resultant normal temperature.

At the time of admission a cause for the profound hypothermia in our patient was not identified. Although sepsis may have been contributory, and aspiration pneumonia was present, the patient's history, physical findings, course and postmortem data do not support an infectious cause for the hypothermia. Similarly, normal deep tendon reflexes and normal thryoid histology make myxedema as a possible explanation for the patient's temperature depression most unlikely. The data very strongly favor exfoliative dermatitis as the prime etiologic factor for hypothermia in this patient. Because the association of hypothermia with exfoliative dermatitis was not appreciated by the medical service, the dermatology service or a consultant hypothermia expert, we feel that this unusual and poorly recognized cause of hypothermia should again be brought to the attention of clinicians caring for patients with erythrodermas.

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Refer to: Belliveau RR, Geiger F.: Lymphocutaneous Nocardia brasiliensis infection simulating sporotrichosis. West J Med 127:245-246, Sep 1977

Lymphocutaneous Nocardia Brasiliensis Infection Simulating Sporotrichosis

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LYMPHOCUTANEOUS SPOROTRICHOSIS presents such typical clinical features that the dermatologist concerned usually institutes therapy long before the results of the fungus culture confirm his clinical impression. On rare occasions these clinical features are mimicked by Nocardia brasiliensis[1-6] and may result in delay of appropriate therapy.

The actual incidence of lymphocutaneous Nocardia brasiliensis infections may be underestimated as a result of two factors. First, Dermatophyte test media (DTM) is a common fungus growth medium used by dermatologists and the antibiotics which it contains (cyclohexamide, gentamycin sulfate and chlortetracycline) may prevent the growth of Nocardia species, as was the situation in this case, and thereby prevent its isolation. Second, a recent report by Mitchell and co-workers[6] has shown that, on occasion, lymphocutaneous Nocardia brasiliensis infection can be cured by therapy with supersaturated potassium iodide (SSKI) alone. This would tend to confirm an erroneous clinical impression of sporotrichosis if no proper culture were obtained. Since five of the previously reported cases were associated with either a prick of a thorn[1-3,6] (four) or working in a garden (one),[4] Nocardia brasiliensis should be considered in the clinical evaluation as a possible, although rare, cause of lymphocutaneous infections in patients who give a history of working around plants.

Report of a Case

A 37-year-old white man was seen by a dermatologist in November 1975 because of an ulcerating lesion of the ring finger of the right hand with associated pronounced swelling of the lymph nodes on the dorsal surface of the wrist (Figure 1) and enlarged epitrochlear lymph nodes. The patient stated that he had pricked his finger on a thorn of a rose bush while working in his garden in Las Vegas 14 days previously. He was treated sequentially with penicillin, ampicillin and tetracycline, but the lesion continued to enlarge despite antibiotic therapy. The dermatologist made the clinical diagnosis of lymphocutaneous sporotrichosis, cultured the exudate on Dermatophyte test media and started the patient on a regimen of supersaturated potassium iodide, two drops three times a day.

Figure 1.—Cutaneous ulceration of ring finger with lymphadenopathy of wrist.

The patient was again seen three days after his first visit, at which time the lesion had become larger. The laboratory reported that duplicate specimens from the lesion had grown a staphlococcus, coagulase positive and an organism tentatively identified as Nocardia. The staphlococcus infection was treated with cloxacillin. Because the lesion was clinically so typical of sporotrichosis,

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and because it was clinically felt that Nocardia was such an unlikely cause of this lesion, treatment with supersaturated potassium iodide was continued.

Eight days after the patient was first seen, the organism was identified as Nocardia brasiliensis and treatment was started with tablets combining 80 mg of trimethoprim and 400 mg of sulfamethoxasole (Septra®), two tablets twice a day. This medication was continued for two months with complete resolution of the lesion. The identification was subsequently confirmed as Nocardia brasiliensis by Dr. Leanore Haley of the National Center for Disease Control in Atlanta.

The characteristics of the organism were as follows:

- Acid fast: positive.
- Hydrolysis of casein: positive.
- Utilization of xantheine: negative.
- Growth in lysozyme broth: positive.
- Production of urease: positive.
- Growth at 37°C but not at 25°C.

Analysis of a specimen of serum showed IgG, 1,075 mg per dl (normal 600 to 1,200); IgM, 190 mg per dl (normal 95 to 125), and IgA, 455 mg per dl (normal 50 to 240).

Discussion

The presentation of this patient with the unusual lymphocutaneous form of Nocardia brasiliensis emphasizes the necessity for utilizing nonselective media in addition to the customary DTM cultures obtained on patients suspected of having fungal infections.

Summary

This report describes the first case of lymphocutaneous Nocardia brasiliensis reported in the state of Nevada, the seventh case reported in the United States and the first case reported in which immunoglobulin analysis of the patient's serum was done. It is easily mistaken clinically for lymphocutaneous sporotrichosis with resultant inappropriate therapy.

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Ergot-Induced Vascular Insufficiency

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During the Middle Ages, epidemic ergotism occurred among people in northern and central Europe following the consumption of ergot-contaminated rye.[1,2] In 1926 ergotamine tartrate was introduced for the treatment of migraine, and now most cases of ergotism are a complication of the treatment of migraine headaches and, occasionally, postpartum hemorrhage.

Three clinical forms have been identified: gastrointestinal with abdominal cramps, diarrhea and vomiting; neurologic with headache, convulsion and coma, and circulatory with ischemia. The vascular complications of ergotism appear to be the result of alpha-adrenergic blockade and direct vasoconstriction.[3] In some instances there may be a toxic effect causing severe endothelial damage, thought to be the result of occlusion of the vasa vasorum. In its severe form, arterial thrombi occur, and ischemic ulceration and gangrene may eventuate.

Report of a Case

A 36-year-old woman with a long history of headaches was seen because of a ten-month history of severe left lower extremity pain. During the past four months her symptoms had worsened, and dependent rubor, swelling and tenderness appeared. Two weeks before admission a small area of skin necrosis developed on her left foot.

Because of a fracture of the ankle one year before, the patient was thought to have reflex sympathetic dystrophy and a posttraumatic pain

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Figure 1. — This arteriogram illustrates the diffuse, symmetrical spasm seen in this patient with severe ergotism.

Figure 2.—Segmental spasm, worse on the left, and almost complete occlusion of the superficial femoral arteries is shown in this study.

Figure 3.—The distal popliteal and tibial arteries were also affected by ergotism; the left side was more severely involved.

syndrome. She had been treated with vasodilators and sympathetic blocks without benefit. During this time she continued to have migraine headaches, and was usually taking ergotamine tartrate daily.

On admission she was afebrile, her blood pressure was 110/62 mm of mercury in both arms and pertinent findings were limited to the legs. Common femoral pulses were reduced, although the vessels felt normal, and no distal pulses could be felt. Thigh blood pressure was 90 mm of mercury, and 60 mm of mercury pressure was measured in the right posterior tibial artery, but no Doppler signals could be detected in the left lower leg. The left foot was swollen without pitting edema, but was tender, cold and cyanotic. Perception of light touch was reduced, and motor function impaired. A 2 cm area of skin necrosis with underlying dark, serosanguinous fluid was present below the lateral malleolus. The foot did not appear viable. A presumptive diagnosis of ergotism was made, with a strong suggestion of secondary distal arterial thrombosis.

Translumbar arteriography (Figures 1-3) confirmed the diffuse, symmetrical spasm of ergot poisoning, and did not show thrombosis, or proximal atheromata. Ergot administration was stopped, heparin and low molecular weight dextran were administered intravenously, and by the following day the patient's condition was much improved. Distal pedal pulses could be felt and Doppler pressures were then detectable. Her condition improved rapidly; the ulcer was debrided and purulent fluid drained. Recovery continued without interruption and the patient was discharged the following week, with no evidence of vascular insufficiency. Muscular function returned rapidly to normal, but hypesthesia in the toes persisted for two months. She has remaincd well subsequently.

Discussion

Three types of ergot toxicity have been described by Bagley and Cooper:[4] acute ergotism following short-term administration of ergotamine tartrate, and thought to be the result of an allergic response; intoxication related to the ingestion of excessively large amounts of the drug; and a chronic form of ergotism in which the patient has been taking the drug for long periods.

Most cases of arterial insufficiency caused by ergot poisoning are easily recognized, occurring in young women being treated for migraine. Pain and paresthesias are early symptoms, and usually occur in the lower limbs, although any or all of the extremities may be involved. Coolness, diminished or absent pulses, pallor on elevation and dependent rubor are also observed. As the ischemia progresses, local tissue necrosis may occur and vesicles appear. Digital gangrene may also eventuate. Findings on arteriography are usually diagnostic, and although scattered diffuse symmetrical vasoconstriction is seen most often,

local constrictive occlusion may occur.[5] The common arteriographic findings usually include symmetrical, smooth, tapered narrowing of major arteries such as the femoral or brachial. Although muscular arteries of the extremities are more susceptible, cases of renal, coronary, mesenteric and carotid involvement have been reported.[6] The proximal vessels are usually free of atheromata, and this finding assists in making the diagnosis. Because of stasis and endothelial injury, thrombosis may be observed, although this is infrequent. Occasionally collaterals may be prominent initially, and regress as the spasm subsides. Why these collaterals in some people are less responsive to ergot toxicity is not known, but their function may favorably influence the prognosis.

Most patients respond promptly to discontinuance of ergot administration. Systemic heparin and low molecular weight dextran may offer some protection from distal thrombosis, and may improve flow in the microvasculature in persons with severe ischemia.[1] Adrenergic blockade is of little value because of the direct effect of ergot, and vasodilators have not been consistently useful, although in some cases benefit has been reported. Immediate and permanent cessation of ergot administration is the cornerstone of treatment and without establishing gangrene the prognosis is very good. If amputation is required, excellent healing of the stump can be anticipated after resolution of the vasospasm.

Summary

Ergotamine tartrate, widely used in the treatment of migraine, may cause severe ischemia with chronic administration. The syndrome is more commonly seen in young women and pain and paresthesias are common manifestations. Arteriographic findings usually are diagnostic, and arteriography is recommended. Cessation of ergot administration is effective therapy, and intravenously given heparin and dextran may be useful adjuncts in patients with severe ischemia.

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Multiple Myeloma Presenting as Ascites

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ASCITES RARELY DEVELOPS in patients with multiple myeloma.[1-6] Even less frequent is ascites caused by peritoneal infiltration with myeloma cells.[2-6] A surprisingly high percentage of those rare patients with myelomatous ascites have had an IgA paraprotein and no bony abnormalities.[3,4] The triad of myelomatous ascites, an IgA paraprotein and lack of bone lesions may represent a distinct clinicopathologic entity.

Report of a Case

In a 57-year-old white woman there was progressive abdominal swelling of one-month duration causing her moderate discomfort. She had been in good health before this time.

She was admitted to hospital for investigation of the cause of the abdominal swelling. Physical examination revealed a grossly distended abdomen with an easily felt fluid wave. No lymphadenopathy, ecchymosis, bone tenderness or abnormality of retinal vessels was present. Laboratory results included a hematocrit of 20 percent and a leukocyte count of 4.2×10^9 per liter with a normal differential. Rouleau formation was not observed. The platelet count was 200×10^9 per liter, the blood urea nitrogen reading was 24 mg per dl; the albumin value was 2.6 grams per dl; the alkaline phosphatase and bilirubin levels were within normal limits. Analysis of urine showed four to five red blood cells per high power field,

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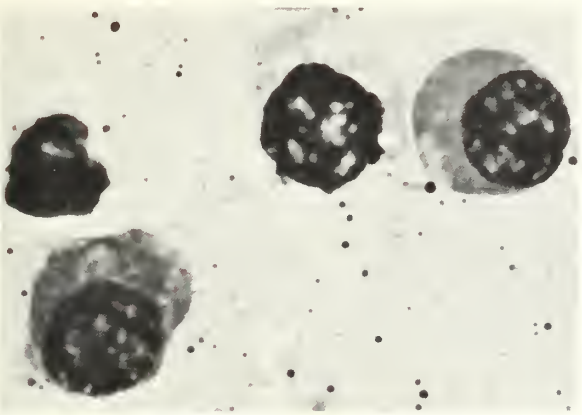

Figure 1.—Representative plasma cells present in the ascitic fluid (Wright's stain).

eight to nine leukocytes per high power field and 2 grams of protein per 24-hour urine collection.

Paracentesis yielded a yellow, slightly hemorrhagic fluid. The specific gravity was 1.028, total protein 2.5 grams per dl, bacteriological and fungal cultures were negative. Wright's stain of a centrifuged specimen of ascitic fluid showed sheets of plasma cells, some having immature nuclei with nucleoli (Figure 1).

The plasma cells in the ascitic fluid prompted further investigations. Bone marrow examination showed 20 percent immature plasma cells with large nucleoli and abnormal mitoses consistent with multiple myeloma. No abnormalities were seen on a roentgenographic bone survey. Quantitative serum immunoglobulin levels were: IgA, 1,100 mg per dl (normal 380±90 mg per dl); IgG, 300 mg per dl (normal 1,240±440 mg per dl); IgM, 29 mg per dl (normal 120±70 mg per dl). Protein electrophoresis on the serum showed a monoclonal peak of 1,010 mg per dl in the gamma region. The urine protein electrophoresis had a 90 mg per dl monoclonal spike in the gamma region. The ascitic fluid did not have a monoclonal peak on protein electrophoresis. The serum, urine and ascitic fluid showed an IgA-lambda paraprotein on immunoelectrophoresis.

Discussion

The appearance of ascites in a patient with multiple myeloma is rare. When it develops, it is usually associated with extensive liver infiltration with plasma cells, infectious peritonitis or myelomatous peritoneal infiltration.[1-6]

Approximately 70 percent of patients with multiple myeloma have plasma cell infiltration of tissues outside the bone marrow.[7,8] The liver is one of the most frequent sites of extramedullary myeloma cell invasion. Thomas and his colleagues[1] reported that liver infiltration with myeloma cells occurred in 40 percent of a series of 64 multiple myeloma patients. Ten percent of the patients in their series had extensive myelomatous liver infiltration and ascites. These patients did not have peritoneal plasma cell infiltrates, congestive heart failure or nephrosis. The authors felt that the ascites could best be explained by postsinusoidal portal hypertension.

Peritoneal infiltration with myeloma cells has rarely been reported to occur in multiple myeloma. In a review of the literature to 1950, Hayes could document only three cases of peritoneal involvement with myeloma cells.[7] Ascites developing from proven myeloma peritoneal infiltration is extremely infrequent.[2-6] Durant and Barry described a patient with multiple myeloma and exudative ascites.[9] The ascitic fluid contained plasma cells. However, peritoneal myeloma cell infiltrates were never proven by biopsy.

Of the six patients, including the authors', established by biopsy or autopsy to have myelomatous peritoneal implants producing ascites, three had an IgA monoclonal spike.[3,4] Of the remaining cases, one patient had an IgG paraprotein, another patient had only Bence Jones proteinuria and in the last case, the type of paraprotein was not reported.[2,5,6] Two of the three patients with IgA paraprotein had no abnormalities on bone survey and the authors of the third report do not mention bone lesions.[3,4] In a review of 869 cases of multiple myeloma seen at the Mayo Clinic, only 24 percent of the patients had an IgA serum paraprotein and 79 percent of the patients had bony abnormalities seen on roentgenograms of the skeleton.[10]

Because of the rarity of myelomatous ascites, it is difficult to know if the triad of myelomatous ascites, IgA paraprotein and absence of bone lesions is mere chance or represents a distinct clinical entity. It is noteworthy that in the lamina propria and base of the villi of the intestines there are abundant plasma cells which secrete predominantly IgA.[11] In mice of the BALB/c strain, when injected intraperitoneally with Freund's adjuvant or mineral oil, ascites and peritoneal plasmacytomas that frequently secrete an IgA paraprotein develop.[12] Bone lesions do not develop in these mice. Patients with alpha heavy chain disease have an IgA heavy chain paraprotein. These patients' predominant clinicopathologic features cen-

ter in the abdomen and they have no destructive bone lesions.[14] It may be that cases with IgA myelomatous ascites represent a distinct clinical entity whose predominant clinical symptomatology is in the abdomen similar to alpha heavy chain disease.

Summary

The case of a patient with ascites produced by peritoneal infiltration with myeloma cells is described and similar cases are reviewed. Of six patients (including the present one), in whom results of autopsy or biopsy showed there were myelomatous peritoneal implants producing ascites, at least three had an IgA paraprotein. Two of the three patients with the IgA paraprotein had no bony abnormalities on skeletal roentgenograms; the third case report mentions no bone lesions. The triad of myelomatous ascites, IgA paraprotein and absence of bone lesions on skeletal roentgenograms may represent a distinct clinicopathological syndrome.

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Removing a Honeybee Stinger

The honeybee leaves the stinger in the recipient. The stinging apparatus is serrated, so that when it sticks in, it's stuck there. It's stuck like a fish hook. And the honeybee merely flies away, leaving part of the venom sac and part of the intestine along with it, and this makes it rather hazardous, because frequently the person stung will try to get rid of this stinger, because it does sting. And this only adds to the insult by injecting more venom than if it had been left alone. And sometimes physicians or first-aid personnel attempt to get hold of the stinger and remove it, and in so doing they press more venom out of the sac and only add insult to injury. So that in removing the honeybee stinger, using a sharp knife or a fingernail just to flip it out is the ideal method.

—RUSSELL I. WILLIAMS, MD, *Denver*

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Adenoma in the Small Bowel

To THE EDITOR: The case report in the July issue describing carcinoma arising in Crohn disease [Burbige EJ, Bedine MS, Handelsman JC: Adenoma of the small intestine in Crohn disease involving the small bowel] is interesting. However, to add to the value and legitimacy of the case, before it becomes entrenched in the folklore of regional enteritis, documentation of the neoplastic changes would be worthwhile.

The photograph submitted is unconvincing, in my opinion. No pathologist is listed in the case report to lend credibility to the diagnosis. These flaws combine to allow skepticism about an otherwise nice case study.

DAVID A. MULKEY, MD
Associate Pathologist
Southern Nevada Memorial Hospital
Las Vegas

* * *

Dr. Burbige Replies

To THE EDITOR: I wish to thank Dr. Mulkey for his comments and commend him for his concern and vigilance.

Unfortunately, it is not always possible to include detailed pathologic material in a simple case report. The case was reviewed by at least two pathologists at The Johns Hopkins Hospital. I will be happy to obtain a slide and forward it to Dr. Mulkey for his review.

EUGENE J. BURBIGE, MD
Assistant Professor of Medicine
UC Davis, School of Medicine
Assistant Chief, Gastroenterology
VA Hospital, Martinez

Multiply Injured Patients

To THE EDITOR: It was with interest that I read the Trauma Rounds' article "Initial Evaluation and Treatment of Multiply Injured Patients" in the May issue. I have become accustomed to reading and learning from Trauma Rounds and appreciate the efforts of Drs. Trunkey and Blaisdell and their staffs in preparing this series. I would like to comment on several aspects of this recent article.

The article described a patient with obvious head, facial and chest, and possible abdominal, injuries who was both hypotensive and tachycardic. It quite appropriately focused on the ABC's of initial management; however, I was bothered by the impression the article gave relative to the management of the airway by orotracheal intubation. I realize a lengthy discussion of decisions that go into the airway management of an acutely injured patient was beyond the scope of this article. but the danger of permanent cervical spinal cord injury while orotracheally intubating a patient with an unstable cervical spine fracture cannot be overstated. I feel strongly that until it can be definitively ascertained by radiographs, patients with evidence of head or facial injuries should be assumed to have a cervical spine fracture and their airway managed by nasotracheal intubation, cricothyroidotomy or Ambu bag and mask. This possibly fatal mistake is too important to be omitted from an article on the management of traumatized patients.

I couldn't agree more that an unstable patient with evidence of thoracic injury should undergo closed tube thoracostomy prior to x-ray.

As to the emergency management of patients in hypovolemic shock secondary to abdominal injury, I would like to relate that our experience with the use of Medical Anti-Shock Trousers (MAST) can be characterized as nothing but

favorable. On multiple occasions (as literature well documents) we have seen a dramatic rise in the systolic blood pressure within moments after the inflation of this suit. While this must not preclude definitive operation, it does in many cases remove patients from shock and maintain them while they are being prepared for laparotomy, thereby avoiding many of the sequelae of the shock state. The use of the MAST can have a net negative effect unless several potential problems are borne in mind. Its use precludes intravenous infusion via the lower extremities and thus necessitates several upper extremity lines; its use markedly elevates the diaphragms, and closed tube thoracostomy must be performed through a higher intercostal space and with much greater care; and perhaps the greatest risk is an unfounded feeling of confidence by the physician resulting in delays in definitive management and underestimation of volume requirements.

MARK E. JERGENS, MD
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Los Angeles

* * *

Dr. Trunkey Replies

TO THE EDITOR: I very much appreciated reading Dr. Jergen's letter. The first point, about the awareness of the cervical spinal cord injury, is an excellent one. In fact, in every patient who is in this category at San Francisco General Hospital a lateral cervical spine film is taken before the patient is moved on to the emergency-trauma table. An exception to this is when a patient comes in with cardiac arrest. In that instance, the anesthesiologist usually maintains the patient's head in an axial alignment and moves right along with the intubation.

In regard to the second point, on the use of Medical Anti-Shock Trousers (MAST), I am also in full agreement. We have previously commented on the use of this device in an earlier Trauma Rounds (Lim RC: Abdominal vascular injuries [Trauma Rounds]. West J Med 123:321-324, Oct 1975).

DONALD D. TRUNKEY, MD
Associate Professor of Surgery
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San Francisco General Hospital
Co-Editor, Trauma Rounds

Pseudoacetylcholine

TO THE EDITOR: Dr. Morris Vilkin's letter to the editor in the July issue is entitled "Grip Test for Pseudoacetylcholine" and discusses patients with "high titre of pseudoacetylcholine." This is physiological nonsense and I am surprised that the editors allowed it to be printed without correction.

There is, of course, no such thing as pseudoacetylcholine. The abnormal sensitivity to succinylcholine found in some patients is due to a genetic deficiency in the plasma cholinesterase enzyme also known as pseudocholinesterase. The "pseudo" prefix is used because it is not the same enzyme as the cholinesterase which is present in nervous tissue and erythrocytes and which is highly specific in its action, the hydrolysis of acetylcholine.

Pseudocholinesterase on the other hand, promotes the hydrolysis of several choline esters including succinylcholine. In its absence, therefore, the action of succinylcholine is greatly prolonged with the resultant syndrome of persisting weakness of respiratory and other muscles.

Dr. Vilkin's grip test may be a valid screening technique for plasma cholinesterase deficiency. But to allow expressions such as "high titre of pseudoacetylcholine" to appear in print in the pages of a scientific journal can only promote confusion and misunderstanding about a subject of considerable importance.

EPHRAIM KAHN, MD
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California Department of Health
Berkeley

Health Care Costs

TO THE EDITOR: I usually find the editorials in the WESTERN JOURNAL astute and throught-provoking, but two that appeared in the June 1977 issue had some serious lapses.

In the first editorial, "Health Care Costs—A Call for AMA Leadership," it is stated "In the not too distant future the rising costs of the nation's health enterprise will equal or exceed the portion of the gross national product (GNP) that can be available for this purpose. In the opinion of some responsible persons this will happen when health-related costs reach approximately 9 per-

cent of the GNP." Who says this is all we can afford and on what data is this based? As long as we continue to spend more money on alcohol and cigarettes than on physicians' services, there seems to be a little more leeway for spending on health. I am not saying that there is not a lot of "unnecessary" expenditure currently in the medical field, but setting an arbitrary limit is silly. An individual should be able to decide for himself how much of his budget he wants to devote to his health (or vices, or rent or whatever he chooses). The problem comes with people who have no money and so the government pays their bill; that is, taxpayers must pay for the care of the indigent before they can make decisions as to their personal budgets.

This leads to a second error: "Unless something is done quickly in the private sector the government will soon have no alternative to imposing a crude and even brutal cap on the money spent." No alternative? Is the author serious? Does he forget that the government makes its own rules? It can make all kinds of alternatives. A few examples might be the following: shift funds from tobacco price supports to public health education, eliminate the terribly cost ineffective Veterans Administration and Indian Health programs and buy all the recipients private health insurance, or eliminate Medicare or Medicaid, or both (that is, reduce the medical care of those groups for whose care it promised to pay, instead of reducing the care of everyone).

The AMA should provide leadership, all right, but a large part of its effort should be education of the public and government, as well as the leadership of organized medicine. This may eliminate the use of the term "inflation rate for health and medical care" (such as used in the editorial "The Federal Trade Commission and Health") when "cost increase" is what is actually meant. Most of the increased cost is for additional or improved services and that's not inflation.

Overall the two editorials were good, but these lapses indicate that maybe the author has been talking to the bureaucrats so long that he is beginning to think like them. Raise your guard.

JAMES T. HAMILTON, MD
Madera, California

Laetrile

TO THE EDITOR: I commend you on the timely article on Laetrile in the July issue [Lewis, JP: Laetrile (Informed Opinion). West J Med 127: 55-62, Jul 1977]. Unfortunately our public is bombarded by quacksters promoting fad diets, vitamin regimens, medications, etc. Since all of these things are garbage, information on them is not to be found in our leading medical journals.

The physician is left to sort through newspaper articles, *Time* magazine, etc. to formulate an opinion. Recently I was discussing Laetrile with an attorney. Although in my own mind, I had reason to believe that Laetrile was worthless, I had no good scientific reference to back up my statement. He will now receive a copy of your article on his desk.

ROBERT A. McCORMICK, MD
Redlands, California

Special Article

Refer to: Kane RL, Wilson, WM: The new health practitioner—The past as prologue. West J Med 127:254-261, Sep 1977

The New Health Practitioner — The Past as Prologue

ROBERT L. KANE, MD, AND WILLIAM M. WILSON, PhD, *Salt Lake City*

The training and utilization of New Health Practitioners (NHP's) has moved within a decade from a small tentative beginning in the mid-1960's to a major health manpower policy issue. Its discussion transcends a number of important and emotionally charged areas including the role of various professions in providing health care services, the renaissance of primary care, the geographic and economic maldistribution of medical services, and the cost of care. It is valuable to highlight what is known, what is professed and what needs to be studied further about this issue.

IN ORDER TO appreciate where we are, it is necessary to have some sense of where we have been. New Health Practitioners (NHP)* actually have been utilized for some time, both in this country and in a number of developing nations where nonphysician practitioners are the only mode of health care delivery for large areas.[2]

The formal training of NHP's within the United States did not really gain national support until the mid-1960's. Yet, again, such training and utilization efforts were not new, even in this country. The Frontier Nursing Service developed by Mary Breckenridge in 1952 to provide midwifery and health education to the people of eastern Kentucky, was perhaps the first formal American effort to train and use physician's assistants. It currently maintains a chain of nurse-run outpost clinics designed to provide primary medical care.[3] Moreover, as long ago as the 1930's, former military corpsmen received on-the-job training in federal prisons to assist overworked prison doctors (according to Mr. R. Bunker, Acting Director, Physician's Assistant Training Program, Medical Center for Federal Prisoners, Springfield, Missouri, in a personal interview, March 15, 1977).

Gradually investigators and commentators began to suggest[4-7] publicly what practicing physicians had known for years: (1) that nonphysician personnel in general medical practice can effectively carry out certain traditional functions as well as most physicians; (2) that such delegation of tasks extends the potential effectiveness of a physician by allowing him more time for patients with greater needs and for participation in preventive and community health activities,

*At the risk of being flayed as male chauvinist foes of nursing, we are going to use some terms for the sake of convenience even though they appear value-laden. The generic class of Physician's Assistant (PA), Nurse Practitioner (NP), Medex and the like will be called "new health practitioners" (NHP) and will be referred to with a male pronoun, except that specific references to nurses will use the female pronoun. The difficulty in finding a term which adequately encompasses without offending is testimony to the confusion in the field today.[1] Nurses vehemently reject any term that describes them as extenders of physician practices, as will be examined in the text. The term NHP is used here only as a tool of convenience, not as any endorsement of a concept. We recognize that NHP's are no longer new. The very need for an explanation like the foregoing indicates the extent to which the subject we are dealing with is emotionally laden.

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and (3) that nonphysician personnel are surprisingly well accepted by patients in these more responsible roles. Almost every physician, and particularly those in the more remote areas, has trained his office staff to assume major clinical responsibilities, although these functions may not always be codified or even made explicit. Frequently office assistants with no formal training may be called upon to triage patients, separating the very ill from the less sick. They may handle telephone requests for advice and when the doctor is away, they may provide some degree of immediate support. Other types of health professionals are also frequently drafted to offer assistance. Local pharmacists may be called upon to prescribe or advise as well as to dispense. While continuing to handle their preventive functions, public health nurses may be commandeered to treat patients.

The current movement to make use of assistants to provide some of the services traditionally rendered by physicians may be said to have begun in 1965 with the development of a program for physician's assistants at Duke by Dr. Eugene A. Stead and the beginning of the Pediatric Nurse Practitioner program at the University of Colorado by Dr. Henry Silver in the Department of Pediatrics and School of Nursing.

Although several individual nurse practitioner programs were developed and evaluated during the next several years,[8,9] 1969 looms as the next critical year in this abbreviated history. In that year the American Medical Association invited the nursing profession to play the role of physician assistant (PA) and was rebuffed stoutly. From that point on the lines were drawn (often obscurely) between what has been called the illness model (medical) and the health model (nursing) of NHP practice.* This question of whether the NHP is a surrogate/support for the physician or a new form of health practitioner capable of autonomous activity remains an important and hotly contested policy issue.

Issues Around NHP's

The initial enthusiasm for NHP's can be attributed to the marketing campaigns and packaging that were developed for the product. NHP's were hailed as the solution to a variety of perplexing problems. Virtually with one blow they were offered as (1) a vehicle for correcting the maldistribution problem by providing services in underserved areas, (2) a source of needed manpower for primary health care services, (3) a means of cheaper care (both to train and to utilize) and (4) a source of employment for returning Vietnam war veterans.

Now a decade later we look out to see a slightly different environment. The predicted doctor shortage now threatens to become a physician surplus, since specific federal legislation (PL 94-484) has been enacted to encourage large numbers of new doctors to enter primary care. At the same time, the costs of care continue to escalate faster than the gross national product. At such a moment it is useful to see which of the issues surrounding NHP's have been resolved and which remain open.

Perhaps the most volatile is still the question of semantics. At present, claims are being laid to the territory vaguely demarcated as primary care with the speed and enthusiasm of the Oklahoma land rush. The varying definitions offered by medicine and nursing about their respective roles, and those of NHP's, adds another dimension to what has become a multidimensional matrix. It is ironic that although the various forms of NHP's may appear to be very different in function, and may even be trained differently, in fact they seem to be more alike than dissimilar in practice. Moreover, the differences, where they occur, seem to be as much due to some combination of practice environment and professional interest as to any specific training effect. Nonetheless differences in training and background produce students with various labels and seem to directly impact the NHP's self-image.

Training and Role Definition

The NHP traces his lineage to two professions: medicine and nursing. His strength lies in the synthesis of these two but he is vulnerable because of the antagonism between them. It is, consequently, very apparent that the NHP movement currently suffers from a growing conflict between the two parent professions. The problem lies not in what the NHP does, but, instead, in the way the NHP perceives himself and is perceived in his health care delivery role.

In general we can say that PA's have been trained by representatives of medicine and nurse practitioners (NP's) have been trained by nurses. While all available data show little difference in the quality or scope of performance of PA's and NP's working in similar conditions, there are

*For a more complete discussion of the early history of the NHP movement and the schism between medicine and nursing see the monograph by Sadler, Sadler, and Bliss.[10]

important differences in their perceived roles and the goals they pursue. These differences are directly attributable to the self-image conveyed by the dominant educating profession.

Medicine views the PA as an extension of the physician—a paraprofessional who can fulfill many of the tasks usually carried out by the doctor. In contrast, nursing sees the nurse practitioner as a means of extending the profession into more direct responsibility for primary patient care, but with a very definite orientation towards maintaining a clear identification with the traditional values of nursing. This value system emphasizes *health* care as opposed to *medical* care, putting heavy emphasis on prevention and counseling. The NP is not content to have responsibilities delegated to her by the physician. This difference in emphasis, together with the need of nursing to retain its identity as a profession separate and distinct from medicine, accounts for most of the difference in performance between NP's and PA's. The contrast lies in the ethos they have absorbed, not in the skills they have acquired.

The role of the NP is further confused by two additional factors. Unlike the PA, the NP does not appear on the scene as a new entity. She is frequently viewed as an extension of the nurse's traditional role and as such may lack a clear identity of her own. Physicians and patients (and other health personnel) used to dealing with nurses in one way now are asked to readjust their thinking in order to recognize the NP as a new health professional. Such a change in tradition is, of course, never readily accomplished without sustained effort and some indication that such change is justified.

The second difficulty sometimes encountered by the NP is reflected in the shift in pronoun made in the previous paragraph. Most NP's are women and are thereby caught up in a morass of stereotypic thinking and behavior even in the midst of the women's liberation movement. We do not mention this fact to condone it, but rather to emphasize that even in our enlightened era sex prejudices continue to exist, particularly when they are associated with stereotyped roles like that of the nurse. Probably the worst experience with NHP's has occurred when an office nurse leaves a practice to acquire NP training and returns with a new set of skills and a new self-image which is not shared by her colleagues.

The health focus of the NP poses a dilemma shared by all concerned about the role of prevention, but it is a special problem for a group whose identity depends on success in this area. Perhaps this is best summarized in the words of one nurse practitioner:

> We are in a quandary currently as to who will pay for the time it takes to provide preventive services. We are in a state of flux in terms of how to best prepare a provider to make decisions for providing these services in a much shorter period of time compared to traditional nurses and physicians. Before we resort to our usual slogans like "an ounce of prevention . . ." or "sugar and spice and . . ." and then continue our business as usual, we should examine the larger determinants—both overt and covert—of the behaviors of providers and consumers.[11]

Legal Status

The role confusion of the NP and PA is reflected in concerns about their legal status. The legal limitations on the functions of NHP's represent a social codification of professional interests. The legal status of NHP's consequently, is controlled by the medical practice and nurse practice acts of each state. More than 40 states have enacted legislation governing the utilization and supervision of physician's assistants and 21 have adopted specific statutes for nurse practitioners during the past six years.[12] Every law governing physician's assistants requires physician supervision. The wording of the North Carolina statute, for example, is typical of the language and intent of most such laws. It reads:

> The assistant must generally function in reasonable proximity to the physician. If he is to perform duties away from the responsible physician, such physician must clearly specify to the Board those circumstances which would justify this action and the written policies established to protect the patient (North Carolina General Statutes, 1971).

While national nursing organizations and some nurse educators have loudly and frequently proclaimed the professional and legal independence of nurses and have resisted all attempts to equate nurse practitioners with other NHP's, especially physician's assistants, it is unlikely that they will be able to overcome the professional, political, legal and economic barriers that currently prohibit them from competing with physicians in the private practice of medicine.[12] As Blair Sadler, a noted legal analyst of the NHP movement, has concluded:

> To advocate, as some organizations have done, that certain professions should be legally independent and receive no supervision from medicine is a grave mistake, because it is on a collision course with increased func-

tional independence. The price of statutorily prescribed legal independence for nurse practitioners or physician assistants will be laws that are very strict and define with too much detail exactly what tasks can be performed and under what circumstances—a high price indeed for an "independent" straitjacket.[13]

Open and Closed Issues

In the decade since the new health practitioners movement got underway much information and experience have become available. It seems almost tautologic to say we know far more now than we did then. For many observers, several of the issues that loomed as important questions have now been satisfactorily resolved. However, others concerned about our knowledge of new health practitioners in the past point out that by far most of our information comes from two types of sources: (1) small intensive studies of a few persons from which only tentative generalizations are possible, or (2) broad national surveys which rely on self-reported information. To the purist neither of these sources is particularly satisfactory; yet because the reported findings seem to confirm our own individual experiences, we have come to accept them as valid despite their methodologic deficiencies.

Today it is safe to say that there are indeed a number of closed issues regarding NHP's. If they are not proved conclusively, they are at least not hotly disputed. These closed issues would include patient satisfaction, quality of care and physician/employer acceptance. Patients have been very accepting of and satisfied with the care rendered by different kinds of NHP's. The quality of care delivered by NHP's, by whatever means we can measure this elusive concept, has been shown to be equivalent to that rendered by physicians working on similar problems.[8,9,14-16] Those sites that have engaged an NHP have usually found it to be a satisfactory experience as reflected in the retention rates of about 80 percent. NHP's have been accepted into a variety of settings including both office and institutional practice, solo and group. The potential job market is much less clear. A few studies have attempted to explore attitudes of potential employers,[17,18] but these have several limitations: (1) they pose the question in theoretical terms rather than relate actual experience; (2) they depend on a definition of the NHP's role and status; for example, if a nurse clinician is uncomfortable as an employee of a physician, her potential market is considerably more constricted than that of a physician assistant who does not share this discomfort; (3) projections from current and past employment rates always threaten to pass the point of market saturation.

Despite optimistic reports anecdotal evidence suggests that there are a number of NHP's looking for jobs. In the decade of the NHP movement there has been a major shift in the manpower environment; fears of a physician shortage have given way to projections of a possible physician excess. The attitudes of physicians toward NHP's are generally positive but the motivation to hire one will depend upon market pressures.

One of the motivating factors for at least one group of NHP proponents, third-party payors, has been the assumption that substituting NHP for MD manpower would result in substantial cost savings. Projections done for prepaid group practice situations appear to support this contention,[19,20] but as Reinhardt has suggested, the true cost of a physician (or physician equivalent) lies much more in the services he causes than in the ones he provides directly.[21] Any augmentation of the physician manpower pool is thus likely to be inflationary.

The future of NHP's is closely linked to the general emphasis today on primary care. If the present thrust can be sustained we can anticipate that substantial numbers of physicians will be redirected from subspecialties into primary care. This may well decrease the demand for NHP's except in areas where physicians cannot be enticed. Alternatively, these new physicians may elect to function more as managers, supervising teams of NHP's. However, this team approach will be in direct conflict with cost containment efforts; one thing is clear: team care is expensive.

The National Scene

One of the most frustrating aspects of any attempt to synthesize our knowledge about NHP's is the wide variations encountered. Simple summary statements just do not hold. Clearly all NHP's are not alike. Physicians have mixed motives in working with them. The settings make varying types of demands on the skills of an NHP. The interpersonal interaction of physician, NHP and other staff may vary widely. Given this kind of variation in the ingredients and the recipe, it is not surprising that the dish may be tasty to some palates and not to others. We have found that the most consistent observation across prac-

TABLE 1.—*Current Work Settings of Graduates**

	Percent			
	Physician's Assistants	*Medex*	*Nurse Practitioners (Certificate)*	*Nurse Practitioners (Master's)*
Setting				
Private solo	20	34	54	58
Private group	31	31		
Clinic	12	11		
Private hospital	13	7	18	35
Government hospital	15	9		
Extended Care facility	4	2	1	3
Non-hospital institution	..	..	15	1
Community and home health	..	..	12	9
School of Nursing	..	..	6	31
Other	5	6	5	4
	100%	100%	111%†	141%†
N=	632	274	243	78

*Adapted from Nurse Practitioner and Physician Assistant Training-Deployment Study. Bethesda, Maryland, System Sciences, Inc., Sept 30, 1976. Final Report on Contract No. (HRA) 230-75-0198.

†Reflects multiple work settings.

TABLE 2.—*Self-Reported Activities of Graduates**

	Physician's Assistants	*Medex*	*Nurse Practitioner (Certificate)*	*Nurse Practitioner (Master's)*
Percentage employed	89	96	90	98
Median number of patients seen daily	24	>25	12	11
Median patient care hours worked per week as NHP	48	48	31	39

Note: response rates vary for each item

*Adapted from Nurse Practitioner and Physician Assistant Training-Deployment Study. Bethesda, Maryland, System Sciences, Inc., Sep 30, 1976. Final Report on Contract No. (HRA) 230-75-0198.

tices and programs was variation—but for the most part these were variations on a theme.

The several data sources that describe the national picture are similarly inconsistent. Different studies have been contracted by different agencies; each has a slightly different focus and a different methodology. The resultant landscape of the national scene is therefore more of the impressionist school than that of the realists. Nonetheless the outlines are generally consistent even if the shapes seem a little blurred.

National data, taken from a University of North Carolina study of PA's and a State University of New York at Buffalo study of nurse practitioners, present a panoramic view of some of the differences in the way relatively early graduates representing these different types of NHP's are utilized. Table 1 examines the work setting. Two thirds of the PA's and three fourths of the Medex work exclusively in ambulatory practice settings. Nurse practitioners at both the certificate* and master's level are more likely to hold multiple jobs (one of which is often in a college of nursing).

These differences are further elucidated in Table 2. Medex and PA's spend more time in patient-care activities related to their NHP role and see correspondingly more patients per day. The employment rates cited may be overoptimistic on the basis of the sampling frame used. More recent information from the SUNY follow-up on NP's suggests that only 75 percent of certificate graduates and 45 percent of the master's graduates were employed as NP's.

Distribution

Both PA's and NP's have had a beneficial effect on health manpower distribution. Data regarding the actual distribution of NHP's among the population have only recently been forthcoming. Lawrence and co-workers,[22] the Association of Physician's Assistant Programs[23] and the Government Accounting Office[24] have suggested that some NHP graduates are doing better than others in terms of their willingness to practice in areas which require additional manpower. Although only fragmentary data are available (see Table 3) it would appear that PA's (especially Medex) have been most effectively deployed in rural areas while NP's (especially the certificate graduates) have gravitated to the inner city.

NHP's have been viewed by some as a means of addressing the sociocultural maldistribution. Special recruitment efforts among minority groups offer a means to attract and train NHP's who might be more likely to work with their peers. Table 3 suggests that no type of NHP program has been excessively successful in reaching out to minority groups. As might be anticipated, those further up the academic ladder are less represented with minority trainees.

One area where NHP's could be creatively deployed to meet a major service deficit (in both quantitative and qualitative terms) is in nursing homes. NP's in particular have the combination of skills and attitudes to perform most effectively

*The certificate graduate NP appears to be a dying breed. These programs sprang up as stopgap measures by nursing educators to retrain nurses for the expanded role. They have now almost entirely given way to master's level programs.

TABLE 3.—*Characteristics of New Health Practitioner Graduates**

	Percent Minority	*Percent in Rural Areas*	*Percent in Inner Cities*
Physician's Assistants	12	18	..
Medex	15	37	..
Nurse Practitioners (Certificate)	13	19	31
Nurse Practitioners (Master's)	5	..	..

*Adapted from Nurse Practitioner and Physician Assistant Training Deployment Study. Bethesda, Maryland, System Sciences, Inc, Sept 30, 1976. Final Report on Contract No. (HRA) 230-75-0198.

in this setting.[25] The area of long-term care is one generally shunned by physicians,[26] but this avoidance behavior is as much the result of inability to deal with the important problems presented as a frustration with the setting and the poor prognosis.[27] Some data already exist to show that nurse practitioners, especially when working with social workers, can provide cost-effective care.[28]

Remote Deployment

The role of NHP's in responding to the primary care deficit will in large measure depend on their willingness and ability to remedy the geographic maldistribution of medical care. There are already some very promising models of NHP's working successfully in this capacity. Perhaps the largest set of such experiences comes from Appalachia and spans the pioneering work of the Frontier Nursing Service to the present chain of small nurse practitioner staffed community owned clinics in North Carolina.[29]

The value of NHP's in a remote setting is a direct function of the degree to which they can work without direct physician supervision. This independent role is, in turn, linked to a number of concerns about the relative comfort of the responsible physician, the NHP and the community.

One means of providing the necessary contact to assure responsible care may lie in technology. Experiments with various means of both sound and video communication have suggested that these have a positive effect on the sense of well-being of all the parties involved. The idea that help is instantly available is very reassuring.[30,31] Computers may provide another means of technological linkage. Combined with a system of protocols a computer can continuously monitor NHP performance and assure that predetermined standards of care are followed.[32] The advent of minicomputers makes such technological monitoring financially feasible and provides the supervising physician with increased protection against malpractice.

Public recognition of the value of the remotely deployed NHP is mirrored in the current legislation to permit rural based NHP's to bill federal third-party programs directly for their services. There seems little doubt that deployment is closely linked to reimbursement. An NHP, whether working for a private or a public corporation, must have the means to generate income. Capitation has proven highly unworkable in rural, sparsely populated areas; fee-for-service reimbursement seems a much preferable route.

As we look toward the future the effect of NHP's on the distribution of care is less clear. To some extent it may be fair to say that NHP's have in large measure responded to market pressures. They have tended to locate in areas where there was a demand for their services and a means of retaining them. This market responsiveness is in stark contrast to physician behavior.

But what happens when the NHP movement comes of age? What is to prevent NHP's from assuming the professional prerogatives of physicians, preferring to remain in urban and suburban areas and allowing supply to create demand. We can already see some reasons for concern about this possibility. Nursing has already proclaimed its commitment to professional autonomy. PA's, who were created in the image of physicians but subordinate to them, give periodic evidence of a longing for independent professional recognition.[33] It seems reasonable to anticipate that with this new status, NHP's will fall equal prey to the pressures that draw physicians to urban centers and away from either rural areas or inner cities.

Productivity

The productivity of NHP's is of great interest to a variety of groups including providers and payors. The broad range of interested groups suggests the complex nature of this question. It is hardly surprising then that this remains an unresolved issue. A number of theoretical projections suggest that an NHP's productivity is in the range of 60 percent of a physician,[34] but that assumption illustrates the vagueness of our knowledge; who would accept the concept of a standard physician unit. Our own work has indicated the wide variation in the productivity of practices employing a Medex.[35]

We know that the environment (for example, prepaid versus fee-for-service, solo versus group) will greatly influence the work of physicians; it seems reasonable to expect that environment will also affect NHP productivity. NHP's employed by physicians will serve different purposes than those employed by institutions. Some physicians seek to increase the number or scope of services delivered; some simply seek relief; others are looking for company. Some want to share; some want to delegate; some want to supervise. The institutional administration deciding on the employment of an NHP will less likely be guided by personal needs.

Nor can the question of productivity be separated from reimbursement. NHP's working in a prepaid situation may be freed from this burden; and therefore Record's estimations,[19] although based on very small samples, may be interpreted as the productivity of an NHP in the uncontaminated setting. As such they suggest that the NHP is a cost-effective member of the health-care team.

Several studies would appear to confirm the financial productivity of the NHP's when their services are charged at the same rate as those of physicians.[35-38] Under mandate from PL 93-602 the Social Security Administration (SSA) is currently conducting a national study to examine the effect of alternative payment systems on NHP productivity and utilization.[39] The thrust of the SSA experiment, however, has been to establish some lower level of proportionate charge. Such a move would tend to reduce the marginal benefit of NHP's and to shift their range of activities toward those with lower unit costs. Smith has argued that the fee structure of medical care should be revamped to more clearly align cost and complexity.[40] If this realignment were done independently of who provides the care, a principle of equal pay for equal care would encourage the use of NHP's for those activities most appropriate to their skill level. However, since NHP's have been shown to be competent in most of the activities of primary care, this sphere of appropriateness is broad.

This reworking of payment principles is no trivial task. The concept is appealing but the implications may be appalling to physicians. We lack an adequate taxonomy for ambulatory care services. The present system grossly encourages surgical and technical procedures (such as labratory work). The basic unit of ambulatory reimbursement other than specific procedures is the office visit of varying sizes. The visit approach therefore becomes a time-based fee system. If there were equity of charge per service based on time spent, this could lead to equity of income between NHP's and MD's—a situation not likely to win much support from the latter, particularly if it entailed a payment system based on the former's wage as a move toward cost containment.

The other side of the productivity question transcends the issue of NHP's although it is caught up in much of the rhetoric, especially about nursing. The question is the extent to which NHP's bring a new dimension to health-care delivery. One becomes quickly enbroiled in arguments over the distinction between health care (with its emphasis on wellness) and medical care (presumably based on an illness model). Much of this debate hinges on the role of NHP's in providing preventive health care and health education. Unfortunately, we have not yet resolved this question for health-care delivery in general and adding NHP's to the already confused picture only clouds the issue. If we indeed have a service which is unsalable, associating it with a new type of health provider will not make it more attractive.

Summary and Conclusions

The picture that emerges of the contemporary NHP movement appears hazy and complex. The factors identified by various observers are neither as simple as they first appear nor are they discrete entities. Productivity is closely related to reimbursement and both are linked with questions of cost. Distribution and demand are similarly tied to these issues.

Superimposed on this interlocking network of concerns are other more volatile issues of self-image and the general concern with the place of primary care in the health-care system. As we look back over the brief span of the NHP movement, it is easy to see that we have come a long way. As with other social movements, the pioneers havc been replaced by the settlers and the outposts have given way to institutions. This retrospective analysis suggests that at least some of the original goals of the movement have been met—the NHP has established himself as a real entity accepted by patients and capable of delivering high-quality care.

Other goals are less clearly realized. The effect of NHP's on the cost of care will depend in large measure on how an NHP is paid and how much

he is allowed to do. Simply put, if NHP services are used in place of physician services (either at the same wage rate or less) the net effect should be a savings because of a readjustment of the price structure and lower use of ancillary services like the hospital. If the NHP is used in addition to the physician the effect is bound to be inflationary. Herein lies an important policy dilemma: the goal of increasing access to care (implying that the NHP is additive to the physician) must lead to an increase in cost.

The question of the NHP's effect on the geographic maldistribution may not yet be resolved. Early data look very promising but they must be reviewed with caution. As the market forces shift and NHP's acquire more established professional status with appropriate legal sanctions, they may become increasingly more responsive to the same social pressures which make it so difficult to send other health professionals to the areas of greatest need.

Much of the future of NHP's seems to be caught up in their struggle to establish an identity which is at once independent and responsible. A strong move toward professional autonomy will add new areas of conflict to the health-care system, but it seems almost inevitable that medicine and nursing must clash around this issue. An NHP who can demonstrate his productivity and acceptance is not likely to remain content for long in a subordinate position. The very success of the NHP movement may breed the next generation of interprofessional conflict.

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Commentary

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Where Is the Malpractice Crisis Taking Us?

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There have been several approaches taken to solve the malpractice insurance problem in this country. However, since the cost of malpractice insurance continues to climb, the changes so far have not solved the problem, and more changes seem inevitable. A major change could be the development of a patient insurance plan that would provide compensation for certain injuries related to medical care. The insurance coverage would be centered on hospital care. If certain requirements are met, the plan may not be more expensive than the current tort liability system, and would offer several advantages. In addition to the patient injury insurance, there could be federal assumption of liability for national immunization programs.

MALPRACTICE INSURANCE continues to present a serious problem in health care in this country. The problem is one of increasing cost, possible inequity and, in some locations at times, decreased availability of insurance. Related to the insurance problem are the issues of quality of care and the role of the tort liability system. The increasing cost of insurance, however, is probably the element that will force change.

Cost is determined by the frequency of claims and the dollar amount of the awards and settlements. Both of these factors are increasing at a rate of approximately 10 percent per year.[1] Changes in tort laws probably will not affect these increases significantly.*[2] Therefore, if the cost of malpractice insurance is not unbearable now, in time it will be. Major changes would seem to be inevitable. In the national forum of debate surrounding these issues, many partial and a few sweeping solutions have been proposed. An amalgamation of several ideas will probably emerge as the solution to the current malpractice problem.

Basic Plan

To some observers it appears that a new plan could partially replace the current system. The fundamental element of the plan will probably be the assumption by each hospital of liability for all negligent injuries that occur therein. The plan would be similar in many ways to Sweden's patient injury insurance program. In Sweden, concern for uncompensated patient injuries and a series of insurance reforms led to the introduction in 1975 of a universal no-fault insurance program for hospital patients.[3] Patients are compensated for actual net losses due to injuries or suffering, with the exception of injuries that would occur regardless of treatment, or those that are part of the expected risk of treatment.

A similar approach could be tried in the United States. If so, it might be fashioned in the following way. A claim could be initiated by a patient or on the patient's behalf by the family, or the physician or hospital employees

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*A possible exception is repeal of the collateral source rule, which may save up to 20 percent of premium costs. That would be neutralized in one year, however, with increase in number of claims and size of awards.

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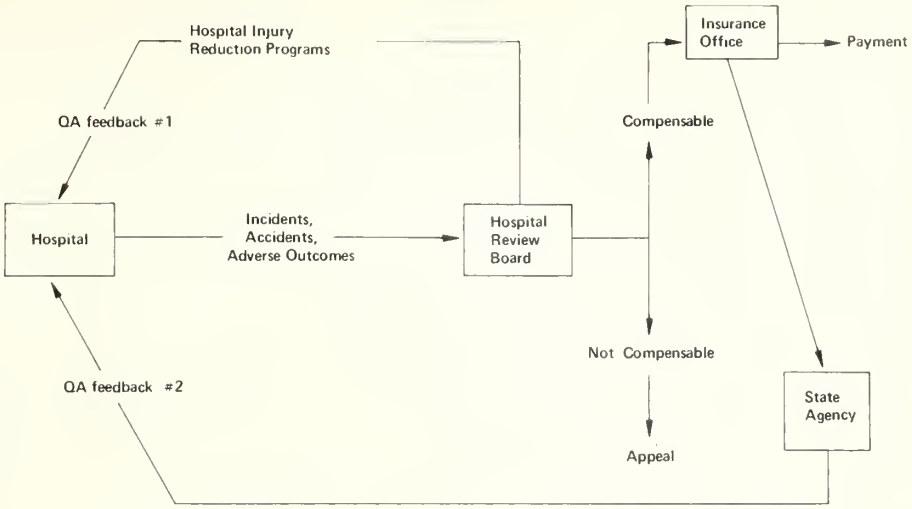

Figure 1.—Diagram of process for handling claims and quality assurance (QA) under patient injury insurance scheme.

(Figure 1). All claims would go to a review board closely affiliated with the hospital (for example, the hospital's Professional Standards Review Organization Board).

The board would review injuries for two purposes. First, to consider how the quality of the care related to the injury could be improved in the future. Such a quality assurance aspect would operate whether or not negligence or malpractice occurred; it could be considered as a self-adjusting, self-improving hospital quality-of-care program.

The review board's second function would be to determine whether the injury was compensable. All injuries would be compensable except those occurring as a result of disease or self-infliction, or as part of the expected risk of treatment. Notice of a compensable event (if that were the determination) would be sent to two separate locations: an insurance office and a state agency (for determination of possible negligence).

The insurance office would pay for actual damage immediately. There would be no defense costs, payments being essentially automatic, and the awards would be made according to a schedule of payments. Such a schedule would include awards for pain and suffering.

The state agency would separately and independently investigate compensable events to determine if negligence had occurred. It would have the authority to institute sanctions against hospitals and physicians. These sanctions could range from mild reprimands to partial restriction of activity or to revocation of license. For example, Medical Liability Mutual Insurance Company of New York, a doctor-owned company, already has a claims committee which reviews loss experience. The committee can exercise economic sanctions against aberrant physician policy holders.

Supporting Plans

Two other plans could support the basic plan. The first one would be the direct federal assumption of liability for certain national immunization programs.

A recently passed federal law now provides that the federal government will be the exclusive defendant for liability related to inoculations against A-New Jersey-76 influenza (swine flu).[4] While this new law represents a major involvement in health care liability for the federal government, it probably does not represent a clear precedent. Under this law, claims are handled in the federal court system. In the future, other similar programs will probably substitute a no-fault compensation plan. Persons who feel they have suffered damage as the result of inoculation would file a claim directly with a federal agency. Malpractice or product liability need not be proven. The only requirement would be that the damage be the direct result of the inoculation. Awards would be given according to a schedule. Coverage under this plan could be extended to any nationally supported immunization program. The plan would be similar to the hospital plan in that both are no-fault and provide compensation according to a schedule.

The other supporting plan would cover that liability remaining after the hospital and immunization program plans have been carried out.

The uncovered liability beyond these programs would be for nonhospital and nonimmunization program care; that is, regular office-based care. Such care is beyond the reach of hospital based quality control mechanisms, and liability would be covered by separate private insurance. Claims would be handled through the tort system. In other words, the system in use today would remain intact for this limited area. Physicians would maintain their own individual liability insurance for activities outside the hospital. However, the premium for such coverage would presumably be inexpensive, since the majority of injuries occur within a hospital.

Advantages

If the hospital compensation plan were implemented, it would represent the imposition of a major new system to replace the existing traditional system for compensation of injuries related to hospital care. Such a hospital plan would offer several potential advantages:

Individual Rights and Equity

The individual patient would not give up the right to representation by attorney. Any decision in the process might be appealed in a manner similar to Workers' Compensation appeal cases. On the other hand, the patient need not have an attorney, and many small claims presently not accepted by attorneys could be processed. This would result in more small awards being made under this system than under the current system. In addition, equity of payments for equivalent injuries could be guaranteed; that is, equal injuries would receive equal compensation. The mechanism would also return a much greater percentage of the system's financing costs to injured patients' benefits.

Prompt Payment

The processing of awards would be prompt, thus improving patient satisfaction and satisfying a desire of society.

Preservation of Insurance Concept

The most general concept of insurance is that it is a mechanism to compensate for damages, without regard to fault. Liability insurance, however, deviates from this concept in that payments are made only if fault (liability) is found. The proposed system would consist of general insurance taken out in the patient's behalf by the hospital. If unnatural or unexpected damage is suffered, the patient would receive compensation. In addition, the system improves the financing aspect of insurance by broadening the risk base. The costs would be spread from the narrow numerical base of practitioners to the much broader base of hospital bed days.

Cost Control

The system would not necessarily be more expensive than the current tort liability system. Cost control would come about in four ways:

- Collateral Sources. Awards under this system would be for actual damages, after other sources of compensation have been considered. Therefore, any compensation from health insurance or unemployment insurance would be subtracted from the total damages allowed.
- Annual Payments. All awards in excess of $100,000 must be made on an annual basis instead of as a lump sum. Such payments may well be for life, which would protect injured patients. It would also allow the insurer to purchase an annuity policy for the victim, usually at a cost less than the lump sum award.
- Schedule of Payments. Awards, as in Worker's Compensation, would be determined according to a schedule. This would provide rational limits on awards, including those for pain and suffering.
- No Defense Costs. In a typical case under the current system, the injured patient brings suit against the hospital, anesthesiologist, surgeon, and possibly others as well. Each must develop his or her own defense. Under the new system there would be little or no defense costs in most cases.

Quality Assurance

Quality of care should be enhanced under the system by two mechanisms. The first is the hospital review board feedback. The review would consider all aspects of hospital operations that could contribute to imperfect results, without regard to negligence. The recommendations of the review board would be implemented by the hospital administration and staff as an "injury reduction program." Such programs might include special training of nurses, improved patient identification mechanisms, and alterations and improvement in hospital equipment.

The second quality assurance mechanism would be the responsibility of the state disciplining agency. This agency, usually the licensing

board, would apply sanctions according to the need. The sanctions could be temporary or permanent. The goal of the agency would be to prevent injuries from occurring in the future.

Further, the assumption of the liability by the hospital retains the costs within the system which is responsible for the expense, rather than divesting the financing directly to such external mechanisms as taxes. This provides a direct financial incentive to the hospital to improve care and prevent injuries.

Individual Physician Liability

Physicians would be kept at risk to some extent, although not to the extent they are at present. All physicians, through hospital staff fees, would be required to share in the cost of the hospital insurance premium. Because of this, some physicians now in a low premium class may pay more, while those in a high premium class may pay less than under the current system. A physician's share of the hospital premium could be based on hospital usage, such as the number of patients admitted each year. This financial interest in the hospital premium would encourage all physicians to participate in the hospital review board functions, and would provide peer pressure to prevent further injuries.

Health Care Research

The records of individual review boards and state agencies could be made available to research groups on an anonymous and confidential basis. Such groups could study health care and indicate areas in greatest need of improvement. For example, physician specialty societies might wish to examine injuries related to their specialty, and encourage research in the indicated areas.

Doctor-Patient Relationship

The hospital delivers care as a "team." Errors in care would be a team responsibility. Individual physicians would no longer fear their patients, because action on the part of the patient would be against the hospital, not the individual physician.

Comments

The hospital plan and the prevention plan would remove compensation for many injuries from the traditional tort liability system. The tort system in this country has developed through trial and error over several hundred years. In many ways it serves its purpose well, and serves justice.

However, when the tort system contributes to, or at least does not prevent, costs in a given area from becoming unbearable, then it should be abandoned for that area. There is a precedent in Worker's Compensation laws and no-fault automobile liability insurance.

In the medical malpractice area there are other valid reasons to abandon the tort system, at least in part. One reason is the inefficiency of the tort system. Approximately 70 percent of the costs of liability insurance are consumed in administrative and legal expenses. Only 30 percent reaches the injured patient. When viewed as a mechanism to compensate for unexpected injury, the system is inefficient.

Further, many patients with relatively minor damages receive no compensation at all, since the preparation and pursuit of such cases is often deemed not worthwhile by attorneys. Therefore, for reasons of cost control, efficiency and equity, a shift to the new plan described here could be justified.

It is often said that one purpose of the tort system is to provide a deterrent to negligence. Fear of a malpractice suit probably does contribute to added concern on the part of a physician caring for a patient. It probably also contributes to the unnecessary costs for defensive medicine. Nevertheless, quality of care should remain a paramount concern. The hospital plan above would provide two mechanisms for improving care. The first would be within the hospital and would deal with all aspects of care, whether or not negligence is involved. The second would involve state licensing agencies. It would add vitality to the core function of licensing boards, which, as originally intended when most boards were created at the end of the 18th century, was to protect the public from poor quality medical care.

This solution would relieve the physician from individual financial risk for care given in a hospital. There could be, however, a direct financial incentive to provide high quality care, if desired. This incentive could be established by requiring the physician to pay a deductible amount (for example, the first $500) for every award given to a patient under his care. However, if the award were based on a no-fault concept, there would be an inherent unfairness; that is, physicians working in high risk specialties, specialties where patients are more likely to suffer unexpected damages, would be more likely to pay deductible

charges, even for results which are outside their control. Therefore a physician deductible requirement would probably only be equitable in cases where negligence could be proven, and the attempt to prove negligence would remove most of the advantages of the no-fault approach. Rather than a physician deductible procedure, the physician's share of the hospital premium and the two quality review boards described should provide adequate incentive to assure quality care.

The concept of partial no-fault insurance for medical care has been widely discussed.[5] Havighurst has suggested a mechanism by which certain events, if they occur, could be differentiated from the expected results of a disease or treatment. Such events would be designated as "compensable" without the need to prove negligence. The Swedish patient insurance system has shown the practical feasibility of such a system. It must be emphasized that this approach is not a general no-fault insurance plan; all adverse or unfortunate outcomes will not be compensated. Instead, compensation would occur only for those events that "should not have happened." Injuries that are compensated for probably would be similar to those that now result in an award under malpractice insurance with the current system (that is, injuries that presumably could have been prevented) except that many more smaller claims probably would be paid.

Because liability associated with medical care in hospital would be covered by the hospital plan, it conceivably could be advantageous to individual physicians to keep patients in hospitals longer, or to admit them more frequently, thereby lowering their outpatient liability exposure. However, programs of review of hospital utilization, such as the Professional Standards Review Organization, would be maintained, and would minimize such a consequence.

Legislation to implement this proposal should include measures to protect both the hospital board and state disciplinary agency members from personal liability that might accrue in carrying out duties related to this program. The protection should be absolute; that is, the members should not be subject to suit for slander or other reasons for any action or discussion relating to an accused physician or hospital.

Government indemnification for preventive medicine programs is not without precedent. Governmental intervention in the marketplace is traditionally justified when it is for the common good.[6] The classic example in the health field is government support of vaccination programs; public vaccination is deemed too important to leave to private marketplace forces. The justification for government intervention is easily extended to cover action necessary to assure the successful completion of such programs. Government indemnification of vaccination and other preventive medicine programs is seen by many as necessary to assure the success of such programs.

Government indemnification to assure the success of a program has several precedents. A law passed in 1958 allows the Department of Defense to enter into agreements of indemnification with contractors.[7] The intent of the law was to protect contractors engaged in extremely hazardous activities, in order to assure their involvement in defense work. For similar reasons, the Price-Anderson Amendment to the Atomic Energy Act allows the Atomic Energy Commission to indemnify contractors up to a certain maximum amount.[8] Also, in 1962 Congress authorized the Veterans Administration to indemnify contractors engaged in research into prostheses and related devices.[9] These three laws are precedents for federal indemnification for contractor liability associated with federal programs.

While this report is speculative, it is nevertheless based on input from many sources. Congress will be debating these issues again, and at that time there will be an opportunity to support other alternatives. Unless another plan is presented that has more equity and cost-control potential, we feel the ideas summarized here will prevail in the long run.

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Medical Care

A Benchmark in Cost-Benefit Analysis

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COSTS, RISKS, AND BENEFITS OF SURGERY—Edited by John P. Bunker, MD, Professor of Anesthesia and Family, Community and Preventive Medicine, Stanford University School of Medicine; Benjamin A. Barnes, MD, Professor of Surgery, Tufts Unversity School of Medicine; and Frederick Mosteller, PhD, Professor of Mathematical Statistics, Harvard University. Oxford University Press, New York, NY, 1977; 401 pages, $8.95.

THE TECHNICAL RATIONALES for *Costs, Risks, and Benefits of Surgery* are said to be the rapid increase in per capita expenditure for medical care, amounting to about 10 percent of average personal income; the questions raised by the public and the Congress as to the benefits of such expenditures; and the lack of correlation between traditional measures of health status and expenditures for medical care. Surgery was selected for study because "its discreteness, accomplishments, and cost," make it "particularly suited for cost-benefit analysis." This book is timely because it proposes a rational vocabulary, analytic tools and objective data to replace the unproductive polemic over the too simplistic notion of "necessary versus unnecessary" surgical procedures.

The book is divided into five parts. Part I, "Background and General Principles," contains chapters on the economic and statistical approaches to cost-benefit and decision analysis. How to quantify values, what to include in costs and benefits, who shall decide—these are questions presented in the context of decision theory and illustrated by actual calculations of risks and benefits in medical and surgical conditions. Neuhauser, an economist, concludes a chapter on cost-effective clinical decision-making with his view that "the explicit trading of dollars for lives" must be considered, otherwise "we do not save as many lives as we could." Abt then summarizes some attempts to define specific components of the quality of life (for example, psychosocial costs and benefits such as "grief at loss of body part" versus "reduced worry over proximate death" in surgical treatment of breast cancer). The importance of patient heterogeneity in deciding whether to operate or treat medically is discussed, as are the limitations in applying classic economic theory and methods of analysis. ". . . The reader is cautioned that the answers presented can depend critically . . . on the economic hypotheses employed." McNeil then analyses the sensitivity, specificity and costs of tests in patients with suspected pulmonary embolism or renovascular disease, in relation to the known efficacy of treatment for these conditions. The final chapter in the introductory section illustrates the primacy of physician attitudes rather than objective indications in explaining the tenfold variation in incidence of adenotonsillectomy in different Vermont communities.

Part II begins with a discussion of operations between 1880 and 1942 that were generally accepted without critical appraisal of their rationale and effectiveness and were later discarded. Of special value is the next chapter which summarizes and analyzes 107 recent research papers on surgical treatment for patients with various forms of cancers, cirrhosis, duodenal ulcer, large bowel disease, vascular disease, trauma and other conditions. A third of the papers were based partly on randomized trials, about a seventh consisted of less well controlled studies, and more than half reported findings without a defined comparison group:

> Quantitatively, when tested by randomized clinical trials, about 14 percent of innovations worked much better than the standard, and in about 30 percent more the innovation was regarded as successful. In about 44 percent of the comparisons the standard was somewhat preferred, and highly preferred in an additional 11 percent. Innovations among primary therapy (those intended to cure the patient's disease) were less often highly preferred than innovations in secondary therapies (those intended to reduce complications and speed recovery).

This chapter is worth the time needed for careful reading because it embodies the current state of the art of objectively comparing the benefits and

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risks of proposed surgical innovations with an existing, standard approach. The next chapter is a disappointingly brief and incomplete formulation of factors that comprise "quality of life" as the ultimate benefit of surgical treatment. Subsequent chapters critically appraise the surgical treatments of duodenal ulcer and briefly resurrect the specters of gastric freezing and internal mammary artery ligation as unfortunate examples of what can happen when procedures endorsed by "authorities" are adopted widely despite lack of scientific proof of efficacy.

Part III contains systematic analyses of costs, risks and benefits with respect to herniorrhaphy, cholecystectomy for silent gallstones, elective hysterectomy, operation for acute appendicitis and treatment of breast cancer. The importance of these chapters cannot be conveyed in a brief review. Neuhauser concludes that elective surgical operation for inguinal hernia in men aged 65 years and older actually decreases life expectancy. The reason given for the substantial increases in hernia repair rates since the onset of Medicare is improvement in the quality of life. An analysis of the cost-effectiveness of cholecystectomy for silent gallstones is unfortunately limited to risk of death. Its conclusion is that "the decision to operate for silent gallstones ought not to be based on life expectancy, but should be heavily influenced by other considerations such as the risk of morbidity, and the patient's peace of mind."

Bunker's presentation on "elective hysterectomy" is cogent, substantive and definitive. Thoughtful reflection on the content of this one chapter will reward the reader with a full understanding of the book's overall intent. Neutra then offers a lucid application of cost-benefit analysis to appendectomy, illustrating the consequences of different criteria for the decision to operate or to wait and see.

McPherson and Fox conclude this section by analyzing the differences in costs and clinical benefits of radical mastectomy and simple mastectomy. They conclude that there is no evidence that the more extensive and costly procedure provides any increase in life expectancy, although the aggregate additional expenditure is estimated at more than 100 million dollars per year. In addition, they define the quality of life in its psychic and social aspects as worse after radical mastectomy than that following simple mastectomy.

Part IV assesses the costs, risks and benefits by decision analysis of such new procedures as treatment of end-stage renal disease, coronary artery bypass operations and intensive care. Here the cost factors weigh heavily and the benefits, by any measure, vary widely depending upon the patient, the patient's overall condition and the selection of treatment. The analysis of the cost of intensive care is especially instructive. Bendixen concludes that there is "a thousandfold difference in costs, from one extreme to the other among intensive care unit patient groups, when cost is expressed as the dollar cost of making one surviving patient live for one year." Although the cost is highly variable he concludes that "much of that care shows a highly favorable cost-benefit ratio."

Part V presents the summary, conclusions and recommendations of the editors, joined by Gilbert, McPeek and Seckhauser. After briefly summarizing the rationale of the book and its substantive conclusions, the authors present four predictable recommendations: the need for further studies of surgical treatments; improving and extending our technical capability to do such studies; teaching of economic, social and epidemiological principles of medical care, and improving the public's understanding of medical outcomes and costs through better presentation.

The concluding statement captures the spirit and tone of the book:

> After data are gathered by good methods and carefully analyzed, the scientist or physician needs to advise the client, *here the community* (emphasis added), about the findings. The community takes this advice and tempers it with political, legal, social, and moral considerations and then decides. We should improve our advice so that it will be useful in the decision process.

This book is a landmark scholarly contribution to our understanding of major socioeconomic issues in contemporary medicine. It is the first definitive compilation of cost-benefit analyses that impressively translates the habitual implicit approaches to decision-making and subjective impressions of risks and benefits into explicit formulations which permit objective and rational comparisons of the results of different treatments.

The discussions take much of the heat and nonsense out of the debate over "unnecessary" surgical treatment. Those expecting a book with such a title to throw down the gauntlet to surgeons in communities where the incidence of common operations is unusually high will certainly be disappointed. The authors clearly did not begin

with the preconceived notion that data should be marshalled to support the widespread accusation that too many unnecessary operations are being done. On the contrary, the authors have succeeded in showing the value of cost-benefit analysis in more clearly specifying the risks and benefits that must be considered by individual surgeons and their patients. When these are combined with cost considerations, the formulations become grist for policy considerations at state and national levels.

Some practicing surgeons will probably be irritated by the idea that such secondary analyses of data in the professional literature by economists and statisticians should prompt them, knowledgeable surgeons, to reexamine their own concepts of indications and contraindications, both absolute and relative. Even more upsetting to some is the fact that Congressional committees, state legislatures and medical insurance companies are vitally interested in such research. Yet the types of analyses here presented are models of much more to come. It behooves all physicians to become familiar at least with the intent and major approaches illustrated here. The bibliography contains names of totally unfamiliar journals; but it is in these journals that the seeds of future policy in health and medical care may already be planted.

Conspicuous by its absence is a substantive summary of research on personal values. These are the factors that most severely limit the attempted rigorous analyses by economists and statisticians of costs and benefits. The study of such values is in the realm of social and behavioral sciences, fields not represented among the authors of the several chapters devoted to this subject. The book also makes almost no reference to the substantial literature on outcomes and end results of medical and surgical treatment, including functional and psychosocial components. This vacuum should be filled in the next edition.

The central "problem" that this book addresses is still an assumption: that we are fast approaching the time when national decisions will have to be made as to which procedures will and which will not be made available to patients—that is, paid for by government or private third parties. Yet the entire history of decision-making in medical care is that of a private and very personal joint action by the physician and his patient. It is doubtful that the American public is about to delegate to a regional or national body the authority to arbitrarily preempt the availability of therapy which is perceived by physicians and their patients as potentially helpful.

Policy makers and investigators who supply them with information may decry the willingness of the public to allow medical costs to continue to escalate rather than demanding that larger proportions of these funds be redirected to much more important determinants of health maintenance: improved nutrition, better life style, better mental health services, reduced smoking and the like. Our self-indulgent society seems to want more of both, but when push comes to shove most of the public still opts for more medical care. The point beyond which public expenditures in the United States for medical care will be judged politically to be "too much" cannot be predicted. It almost certainly will not be, as is commonly stated, when they amount to 10 percent of the gross national product. But it is clear that some ceiling or acceptable rate of increase will have to be achieved if a national policy of equitability in access to needed care is to be other than a political slogan. Present proposals by the Administration to impose an arbitrary cap on hospital costs is the only approach that politically oriented minds can conceive of. And it is in recognition of this reality that *Costs, Risks, and Benefits of Surgery* makes its signal contribution: suggesting a long-term rational approach to medicine collectively for moderating cost increases by carefully evaluating new and costly procedures before they are widely introduced. It is a potential answer—and the only one that can come through voluntary action—to the "technological imperative." No arbitrary cost containment programs can work in our pluralistic system. Should we ever have national health care, annual budgeting will then impose the cap long sought by those who are convinced most medical and surgical care is not "cost-effective."

The main message of this book for medicine seems to be directed to those who are in a position to initiate sound scientific evaluations of new procedures before they are generally adopted. The analyses of coronary bypass procedures support the conclusion "that surgery was the optimal course of action for almost all patient types considered." "From the point of view of society's resource allocation, however, coronary bypass surgery appears less attractive. Indeed the cost

per year of life saved (adjusting for changes in quality of life) clearly exceeds levels generally available elsewhere in the health sector . . . ." Finally, "What is optimal medical care for the individual patient may not be optimal when we, as society collectively, consider what it is costing us."

In the past few years the market has been flooded with hurriedly compiled and poorly edited books whose authors were eager to cash in on the growing interest in health policy issues without much regard for the quality of the writing or even the content. In welcome contrast this book sets a strong example for future efforts by those who would advance our understanding of these enormously complex but central issues. The editors and contributors have given medicine a benchmark for determining the contributions of a large portion of surgical treatment to the welfare of individual patients and the American public. They have given policy makers and planners a perspective on costs and risks and on the inadequacy of current formulations for estimating aggregate benefits. I hope work is already underway to improve such analyses and extend them to other major fields of medicine.

Aspirin and the Prevention of Myocardial Infarction

Will aspirin prevent myocardial infarction?

DR. WALSH: "My emotional response is that it offends my scientific sensibilities to a certain extent because I think one has to look for hard-nosed proof in this very difficult area of clinical trial work. The other point I would like to make is that aspirin is not a harmless form of therapy as so many people would propose: 'Aspirin has been around for years, most people take it, and therefore it can't be very harmful.' . . . On the other hand, there is growing evidence, I think, that aspirin administration can have harmful and even fatal consequences. As to bleeding consequences —it is certainly well known that the number of aspirin tablets received correlates very positively with the amount of blood found in stool. The incidence of asthma and other allergic reactions induced by aspirin, I think, has to be reckoned with and I do not think that it is warranted to simply use aspirin treatment in patients without showing that it is effective."

If one does use aspirin as an antithrombotic agent, what is the suggested dose?

DR. FRATANTONI: "Well, of course, the studies are still going on, but in most of the studies the dosage range is somewhere between 600 and 1,200 mg per day. The study being conducted right now by the Heart and Lung Institute is using 1 gram per day."

—PETER N. WALSH, MD, *Philadelphia*
JOSEPH FRATANTONI, MD, *Washington, D.C.*
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Medical Information

Lead in the Blood of California Children

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LEAD IS UBIQUITOUS in the environment, being found in air, water, food, dirt, dust, paint and, as a result of ingestion and inhalation, in humans.[1-3] An excess body burden of lead is associated with a variety of health problems which can have severe individual and societal consequences. The major systems affected are the nervous, gastrointestinal and hematopoietic. The effects on the nervous system range from mild neurological disabilities and hyperactivity to mental retardation and acute encephalopathy.[3] Gastrointestinal manifestations of lead toxicity are loss of appetite, abdominal colic or cramping pain, constipation, nausea and weight loss. The major effect of lead on the blood is reduction in hemoglobin production as well as increased red blood cell destruction.[1,3]

Children, particularly those with pica, the habit of eating nonfood items, are susceptible to an increased body burden of lead. Until recently, it was believed that most of the problems of elevated blood levels of lead in children existed in the East and Midwest, especially in areas of rundown inner-city lead-painted housing.[4] In 1975, the Center for Disease Control (CDC) funded a lead-poisoning prevention program in Los Angeles, Contra Costa and Alameda Counties. The purpose of this paper is to present the data from the first year of that program. The paper is restricted to the screening aspect of the program. A later paper will discuss the other equally important aspects, namely pediatric follow-up, and source identification and removal.

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This study was funded by a grant from the Center for Disease Control, Atlanta.

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ABBREVIATIONS USED IN TEXT

AIHL = Air and Industrial Hygiene Laboratory
CDC = Center for Disease Control
EP = erythrocyte protoporphyrin

The Screening Program

The primary goal of the entire program is to prevent lead poisoning by the early detection of children with increased lead absorption, followed by effective medical and environmental intervention. Consequently, the population groups to be screened were chosen to create a maximum probability of finding children at risk. In almost all cases only children under 6 years old were screened. In Los Angeles, the criteria used to select the census tracts were that 70 percent of the houses were constructed before 1939, a significant number were deteriorating, a higher than average number of families fell below the poverty level and each tract contained at least 500 children less than 6 years of age. Similar criteria were used in Alameda and Contra Costa Counties. After applying these factors, the Watts-Florence-Firestone area in southeast Los Angeles was chosen for lead screening. The area is located between two major freeways and has some heavy industry. Approximately two thirds of the population is black and one third Chicano, with a total population under 6 years old estimated at 13,700. In Alameda County, an area in West Oakland with industry and bounded by freeways (many of them elevated) was chosen. A belt of land containing industry north of Berkeley along the eastern shore of San Francisco Bay was selected in Contra Costa County.

Blood samples were obtained by county health department workers, mostly on a door-to-door canvass. The Air and Industrial Hygiene Laboratory (AIHL) supplied the counties with standardized microcollection kits manufactured by Trace Metals, Inc.* Venous samples were col-

*Mention of commercial products is not to be construed as an actual or implied endorsement.

lected in 10 ml heparinized "minimal lead" Becton-Dickinson Vacutainers®.

In this program, a capillary finger stick sample was usually employed for the initial screen (Contra Costa collected venous samples whenever possible). These micro-samples are easily contaminated by lead, particularly during the collection processes. Comparisons in the laboratory between values obtained by simultaneous finger stick and venous collection showed good agreement under these ideal conditions, but it was not possible to carry out such experiments in the field program.

To reduce errors in identification of children at risk due to contamination, each blood specimen was tested for both blood lead and erythrocyte protoporphyrin (EP), a gauge of the metabolic effect of lead. (Protoporphyrin combines with iron to form heme which, with globin, forms hemoglobin. Lead blocks this process and the excess protoporphyrin accumulates in the red blood cells. EP is usually expressed in micrograms of free erythrocyte protoporphyrin (FEP) as μg per 100 ml of whole blood.) Also, EP is less subject to physiological changes and is a better index than blood lead measurements of potential toxicity from the body's lead burden.[5,6] However, elevated EP levels (above 60 μg per 100 ml) may also be due to other conditions such as chronic inflammation and iron deficiency. According to CDC guidelines, in those children with an EP level greater than 60 μg per 100 ml and a blood lead level greater than 30 μg per 100 ml there should be a follow-up with a second test. The follow-up was usually done by venipuncture.

Measurement Techniques

The specimens from all three counties were analyzed either by the AIHL or the Sacramento County Health Department Laboratory using the same analytical methods. The EP was determined by the ethyl acetate-acetic acid-HCL method of Chisholm and Brown[8] and the concentration read on a fluorometer calibrated with protoporphyrin IX standards. The lead analysis was done by atomic absorption using a modification of the Delves method.[9,10]

Both laboratories participated in the monthly CDC lead and EP proficiency testing program, and AIHL also participated in the New York State Health Department's Lead and EP Proficiency Testing Programs. Blood lead standards which were used by both AIHL and the Sacramento laboratory were prepared quarterly at AIHL using blood from steers that had been fed lead acetate. These standards were analyzed by four reference laboratories outside of California that used three different analytical techniques: Delves cup, carbon-rod atomic absorption and anodic stripping voltammetry. Agreement among the four reference laboratories was excellent. The results of these programs plus a number of "blind" interlaboratory comparisons of split samples indicated that the laboratories were proficient in lead and EP analysis.

Results

The results of the dual screening program for Los Angeles County from December 1, 1975, through August 1, 1976, are listed in Table 1. The blood lead and EP categories were chosen to conform to CDC guidelines.[7] If an initial test yielded a low EP value, but a high lead level, and was followed by another test that showed low lead and EP values, the initial sample was assumed to be contaminated and only the second test was included in the table. A total of 281 children or 23 percent of the 1,239 tested had elevated blood lead and EP (30 μg per 100 ml or greater and 60 μg per 100 ml or greater, respectively). It is important that these children receive follow-up testing to confirm the initial test so that the child can be given appropriate

TABLE 1.—*Results of Dual Screening in Los Angeles*
DECEMBER 1, 1975 TO AUGUST 1, 1976

Blood Lead μg/100 ml	*Erythrocyte Protoporphyrin (EP)—μg/100 ml*									
	<60		*60<110*		*110<190*		*190+*		*TOTAL**	
	Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
<30	431	34.8	86	6.9	13	1.0	6	0.5	536	43.3
30<50	399	32.2	154	12.4	62	5.0	19	1.5	634	51.2
50<80	22	1.8	16	1.3	13	1.0	15	1.2	66	5.3
80+	1	0.1	..	..	..	..	2	0.2	3	0.2
TOTAL* .	853	68.8	256	20.7	88	7.1	42	3.4	1,239	100.0

*Column and row percent figures may not add exactly to totals due to rounding off.

medical care. Unfortunately, some children could not be retested for various reasons. However, of those retested, usually by venipuncture, approximately 60 percent remained in their initial category or went to a higher one. There is no way to show clearly why a child went down in class upon retest, but besides the important possibility of contamination of the initial sample, other causes such as more parental guidance or the elimination of the source, or physiological fluctuations are possible. In some cases there was a delay of weeks or more before a child could be retested. Therefore, the crucial question of what percentage of the children in these particular census tracts in Los Angeles have elevated lead levels cannot be answered with precision. However, based on the 60 percent confirmation rate in those who were retested it is estimated to be at least 14 percent but less than 23 percent.

Similar tables for Alameda and Contra Costa Counties, not presented here, showed fewer children with elevated levels. Contra Costa results showed between 2 percent and 4 percent, while Alameda showed between 6 percent and 8 percent.

Conclusions

The above data show that there are children in California with elevated blood lead levels. The data show problems in Alameda, Contra Costa and, particularly, Los Angeles Counties. Although not calculable with accuracy, the cost to society of neglecting this problem may be phenomenal. We urge, therefore, that the screening program, including initial screening, diagnostic pediatric management, and source identification and removal, be continued in these counties and expanded to other areas.

Summary

An excess body burden of lead in humans is associated with a variety of health problems. Children, particularly those with pica, the habit of eating nonfood items, are most susceptible to an increased body burden of lead. Although elevated lead levels in children have been shown to exist in cities in the East and Midwest, it had been generally believed that no significant problem existed in the western United States. This paper presents data from a lead screening program which utilized a dual test in which both lead and erythrocyte protoporphyrin were measured. The data show that children with elevated lead levels may be found in California, particularly in an area of southeast Los Angeles, where 14 to 23 percent of the 1,239 children screened had blood lead levels greater than 30 μg per 100 ml of whole blood, simultaneous with erythrocyte protoporphyrin levels greater than 60 μg per 100 ml.

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BOOK REVIEWS

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HUMAN NEUROANATOMY (Formerly Strong and Elwyn's Human Neuroanatomy)—Seventh Edition—Malcolm B. Carpenter, MD, Professor of Anatomy, College of Physicians and Surgeons, Columbia University. The Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202), 1976. 741 pages, $25.00.

This is the 7th edition of a well-known textbook of neuroanatomy, produced first by Adolf Elwyn and Oliver Strong, subsequently by Ray Truex and Malcolm Carpenter and now by Carpenter alone. The book has always aimed at a goal of a comprehensive treatment of human neuroanatomy and the present volume is no exception, containing 630 pages of text, an extensive and fairly up-to-date bibliography and an atlas of the human brainstem in both the transverse and parasaggital planes. It is profusely illustrated with drawings and light and electron micrographs.

The organization of the book follows the basic pattern present in all editions. The first few chapters deal with the gross anatomical aspects of the brain and spinal cord, followed by a chapter on the development of the nervous system, then chapters on the neuron and aspects of the peripheral and autonomic nervous systems. The latter two thirds of the book deal with the central nervous system, beginning with a treatment of the spinal cord and progressing toward the cerebral cortex. The final chapter deals with the blood supply of the central nervous system. In general the text is of good quality; the descriptions of various structures are dealt with at length, in many cases resulting in rather slow going for the reader. Although most of the halftone reproductions are sharp and clear, some are blurred and of poor quality.

Neuroanatomy is a cornerstone of neurobiology, a rapidly moving and very important area of modern biological science. Many new techniques in neuroanatomy have greatly improved the anatomist's ability to analyze the organization of the nervous system. Unfortunately, few of these techniques are adequately dealt with in the present textbook. The mechanism of axon transport which underlies the important method of autoradiography, used to assess neural interconnections, and the retrograde transport mechanism shown by horseradish peroxidase histochemical methods, are barely dealt with in this book. This is indeed unfortunate because not only have these methods revolutionized experimental approaches to brain organization, but the mechanism of axon transport itself is crucial to our understanding of neuron function. Similarly, there is very little in the book about modern views of development of the nervous system, the ways in which neurons are generated and form interconnections with one another during development, nor is adequate mention made about current work dealing with plasticity of neural connections during development or regeneration following injuries to the nervous system. Neural development and plasticity are now of great interest in clinical disciplines as well as in the experimental laboratory, and deserve more coverage in a comprehensive text such as this one. The discipline of neuroanatomy is presently growing at an enormous pace which, it is to be hoped, will have important repercussions for clinical medicine in the next few years. The sense of excitement of the discipline is missing in the present volume.

In summary, this is at present the most comprehensive text available in the field of human neuroanatomy. It is reasonably up-to-date in its descriptions of the organization of the peripheral and the central nervous system. It suffers from the lack of adequate descriptions of the mechanisms underlying the most modern neuroanatomical techniques and the relation of these mechanisms to the basic functioning of the brain. Nonetheless, the book is a solid one in its approach to descriptions of brain organization. I would recommend it as an important text and reference work for those in clinical or basic science disciplines in which a knowledge of neuroanatomy is essential.

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RECENT ADVANCES IN ANAESTHESIA AND ANALGESIA—Number Twelve—Edited by C. Langton Hewer, MB, BS(Lond), MRCP (Lond), Hon FFARCS(Eng), Consulting Anaesthetist to St. Bartholomew's Hospital and to the Hospital for Tropical Diseases, London; and R. S. Atkinson MA, MB, B Chir, FFARCS, Consultant Anaesthetist, Southend General Hospital, Essex. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 268 pages, $29.50.

With this edition, Hewer and Atkinson have published the twelfth book of a series that began in 1932. As in previous editions individual chapters have been written by anesthesiologists with expertise in specific areas.

Typical of the essays of current interest is one concerning pollution and the anesthetist. Overall, the author gives a well-balanced review of the problem, pointing out the doubts expressed concerning its magnitude and even the doubts about its reality. For those who are concerned about operating room contamination the chapter has a section on the various techniques for prevention. I found the chapter on the safety of anesthetic apparatus particularly interesting. It is well written and tells anecdotally of problems that have occurred with the various instruments used to administer an anesthetic. The problems are not remote. My colleagues and I have encountered several of the described events. The chapter is reminiscent of presentations that are made at anesthesia clinical conferences. A. R. Hunter has written about new anesthetic drugs. He includes all that have been introduced in the United States in the past six years. He also mentions drugs that are in the category of experimental. The discussion of althesin will be of only passing interest since this medication is unlikely to be released for clinical use in the United States. Further essays reflect the growing interest of anesthesia specialists in areas outside the operating room. Half of the chapter written about recent advances in pediatric anesthesia deals with postanesthetic care. Techniques for administering neurosurgical anesthesia, anesthesia for endoscopy and anesthesia for transplant surgical procedures are well covered.

The book will be useful to practicing anesthesiologists who, although perusing the literature and attending meetings, may have a fragmented grasp of recent developments. The trainee in anesthesia will find the book valuable for synthesizing all that has recently transpired in selected areas. One would have hoped that the recent devaluation of the pound sterling would have made this book less expensive. Alas, it is not so.

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CEREBRAL ARTERIAL DISEASE—Edited by R. W. Ross Russell, Physician to the Department of Neurology, St. Thomas' Hospital; The National Hospital for Nervous Diseases, Queen Square, and Moorfields Eye Hospital, City Road, London. Churchill Livingstone - Medical Division, Longman Inc., 19 West 44th St., New York City (10036), 1976. 323 pages, $30.00.

This multiauthored book on cerebrovascular disease attempts to deal with every aspect of this important topic, from epidemiology to rehabilitation. There are also chapters on the natural history and prognosis of cerebrovascular disease, pathology, experimental studies on the pathogenesis of cerebral ischemia and infarction, cerebral blood flow measurements in stroke, transient cerebral ischemia, clinical diagnosis of completed stroke, the management of acute cerebral infarction, cerebral ischemia and hypertension, spontaneous intracerebral and cerebellar hemorrhage, subarachnoid hemorrhage from intracranial aneurysm and angioma, and the less common varieties of cerebral arterial disease. The book highlights recent advances in these areas, placing particular emphasis on stroke prevention, pathogenesis of arterial degeneration, mechanisms of thrombosis and embolism, diagnostic techniques and therapeutic measures.

As might be expected in a book with 16 authors, there is a certain amount of unevenness. Some of the chapters are informative, providing useful data and discussing new concepts, while others omit important information.

The chapter on epidemiology reviews most of the leading studies on the subject. While it discusses all of the known risk factors in an objective and statistical manner, its concluding statement regarding stroke prevention is both weak and negative. There may indeed not be incontrovertible statistical evidence that weight reduction, change in dietary habits, regular exercise, treatment of existing diabetes and hypertension, and discontinuance of the use of tobacco prevent vascular disease, including stroke. However, it seems more than prudent to vigorously push these measures, since the overall benefit to health and improvement in the quality of life gained by following these procedures seem more than amply documented. The chief hope for effectively combating the scourge of vascular disease and its attendant economic impact on society lies in the effective modification of every potential risk factor undoubtedly including drastic changes in lifestyles.

The chapter on the investigation of stroke discusses all of the newer techniques including computerized axial tomography, thermography and the percutaneous measurement of arterial blood flow using the Doppler principle. The discussion on scintigraphy or isotope encephalography is inadequate, in that it describes only the *static* scan useful in delineating an area of infarction a week or so following its development. It fails to mention the *flow* scan, which is of great usefulness in the detection of areas of hypoperfusion caused by carotid or middle cerebral artery stenosis or occlusion or areas of hyperperfusion seen as a consequence of luxury perfusion surrounding an area of ischemia or infarction in the brain.

In the chapter on transient cerebral ischemia, the topic of anticoagulant therapy is treated in a very cursory manner. The use of aspirin and other platelet aggregation inhibitors should have been discussed in more practical detail.

The chapter on cerebral ischemia in hypertension contains an excellent discussion of arteriopathic dementia. The author makes a point that, although it is well known to most neurologists, requires constant emphasis and frequent repetition: dementia that afflicts elderly patients is *rarely* caused by arteriosclerosis, the majority of cases being due to Alzheimer disease. In the very small percentage of demented patients in whom the disease is thought to be arteriopathic, the responsible vascular lesion is lacunar state and virtually never atherosclerosis of neck or intracranial blood vessels. Lacunar state, which affects small blood vessels, occurs as a consequence of diabetes or hypertension; its clinical course can be distinguished from Alzheimer disease.

The text is generally well written and the illustrations are of good quality. Considering the relatively small amount of new information on cerebrovascular disease provided, the price of this book seems excessively high. There exist domestic texts that deal with the same topic in a somewhat more lucid and straightforward manner, contain more useful and well selected bibliographies, and cost less.

PIERRE M. DREYFUS, MD
Professor and Chairman
Department of Neurology
University of California, Davis

* * *

MODERN STOMA CARE—Edited by Frank C. Walker, MD, ChM, FRCS, FRCS(Edin), Consultant Surgeon, Cleveland Area Health Authority; Hunterian Professor of the Royal College of Surgeons of England; Fellow of the Association of Surgeons of Great Britain and Northern Ireland. Churchill Livingstone - Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 193 pages, $22.50.

A technically excellent operation is necessary, but not sufficient, to restore patients with intestinal stomas to health and happiness. Preoperative and postoperative counseling, education and training of patients and their families all are equally important aspects of rehabilitation which were neglected until recently. These deficiencies and methods to meet them provide the theme for this book. Although some of the proposed solutions are peculiar to the British system of health care delivery, the problems encountered by stoma patients are universal. The formation of lay organizations and the development of enterostomal therapy as a profession have improved the situation, but more needs to be done in the area of community services.

In addition to a discussion of these general considerations, the introductory section of the book contains an excellent treatise on the management of peristomal skin problems. The next three sections discuss colostomy, ileostomy and ileal bladder, respectively. The history, surgical technique, physiologic alterations, prevention and treatment of complications, and management of each type of stoma are presented in detail. Surgeons may argue with some of the recommendations, such as the optimal length of an ileostomy, but in general the advice is sound. The last section describes stoma equipment available in Britain and is not useful for American readers.

The book is authoritative and thorough. The illustrations are clear and simple. The text bears an unmistakable British stylistic stamp and is heavy going at times. The specialized nature of the subject probably limits its appeal to physicians, surgeons and nurses who deal with stoma patients frequently. That is unfortunate, because those professionals who encounter these patients only occasionally would benefit most from reading this book.

THEODORE R. SCHROCK, MD
Associate Professor of Surgery
Director, Ostomy Care Center of San Francisco
University of California
San Francisco

in memoriam

ANDERSON, FORREST N., Van Nuys. Died May 24, 1977 in Cambria, aged 82. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1921. Licensed in California in 1929. Dr. Anderson was a member of the Los Angeles County Medical Association.

AZEVEDO, JOSEPH LEO, JR., Modesto. Died June 4, 1977 in Modesto, aged 77. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1933. Licensed in California in 1933. Dr. Azevedo was a member of the Stanislaus County Medical Society.

BURNS, BEHLE BASIL, Pasadena. Died April 30, 1977 in Pasadena of metastatic malignant melanoma, aged 72. Graduate of the University of Illinois College of Medicine, Chicago, 1931. Licensed in California in 1934. Dr. Burns was a member of the Los Angeles County Medical Association.

BUSH, HENRY CHESLEY, Livermore. Died July 12, 1977, aged 90. Graduate of the University of California Medical School, Berkeley-San Francisco, 1912. Licensed in California in 1912. Dr. Bush was a retired member of the Alameda-Contra Costa Medical Association.

DAVIS, ELIZABETH A., San Francisco. Died May 31, 1971 in Berkeley, aged 87. Graduate of the University of California Medical School, Berkeley-San Francisco, 1923. Licensed in California in 1923. Dr. Davis was a retired member of the Alameda-Contra Costa Medical Association.

EARL, CHARLES N., Arcata. Died May 18, 1977 in Santa Rosa, aged 68. Graduate of the Creighton University School of Medicine, Omaha, 1939. Licensed in California in 1947. Dr. Earl was a member of the Humboldt-Del Norte County Medical Society.

FELDMAN, EDWARD G., Los Angeles. Died December 20, 1976 of myocardial infarction, aged 62. Graduate of the University of Illinois College of Medicine, Chicago, 1939. Licensed in California in 1947. Dr. Feldman was a member of the Los Angeles County Medical Association.

FITZGERALD, JOSEPH D., San Jose. Died June 13, 1977 in Redding, aged 69. Graduate of the Creighton University School of Medicine, Omaha, 1931. Licensed in California in 1960. Dr. Fitzgerald was a retired member of the Santa Clara County Medical Society.

FURBUSH, CLAUDE GILBERT, Oakland. Died June 30, 1977 in Oakland of heart disease, aged 73. Graduate of the University of California Medical School, Berkeley-San Francisco, 1929. Licensed in California in 1929. Dr. Furbush was a member of the Alameda-Contra Costa Medical Association.

HAND, FRANK B., San Francisco. Died July 10, 1977, aged 78. Graduate of the Creighton University School of Medicine, Omaha, 1926. Licensed in California in 1928. Dr. Hand was a member of the San Francisco Medical Society.

HARA, HATSUJI JAMES, Los Angeles. Died May 28, 1977 in Yucaipa, aged 88. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1918. Licensed in California in 1918. Dr. Hara was a member of the Los Angeles County Medical Association.

HARGROVE, J. G. KENNETH, Berkeley. Died June 26, 1977 in Berkeley of heart disease, aged 68. Graduate of the University of California Medical School, Berkeley-San Francisco, 1936. Licensed in California in 1936. Dr. Hargrove was a member of the Alameda-Contra Costa Medical Association.

HAYES, CHARLES MICHAEL, Los Angeles. Died May 28, 1977 in Los Angeles of complications following surgical operation for ruptured aneurysm of abdominal aorta, aged 75. Graduate of St. Louis University School of Medicine, 1925. Licensed in California in 1929. Dr. Hayes was a member of the Los Angeles County Medical Association.

HOUCK, GEORGE HAMILTON, Stanford. Died July 7, 1977 in Palo Alto of heart disease, aged 75. Graduate of Harvard Medical School, Boston, 1927. Licensed in California in 1930. Dr. Houck was a member of the Santa Clara County Medical Society.

IRVINE, RICHARD BOONE, Concord. Died June 10, 1977 in Concord of leukemia, aged 54. Graduate of the University of Southern California School of Medicine, Los Angeles, 1950. Licensed in California in 1950. Dr. Irvine was a member of the Alameda-Contra Costa Medical Association.

KASDAY, HERMAN R., Los Angeles. Died January 11, 1977 in Los Angeles of cardiopulmonary arrest, aged 74. Graduate of Middlesex Hospital Medical School, University of London Faculty of Medicine, 1934. Licensed in California in 1944. Dr. Kasday was a member of the Los Angeles County Medical Association.

KNOTT, JAMES I., San Diego. Died July 1, 1977, aged 75. Graduate of Washington University School of Medicine, St. Louis, 1925. Licensed in California in 1939. Dr. Knott was a member of the San Diego County Medical Society.

KNOTT, NORMAN L., Los Angeles. Died May 31, 1977 in Altadena of heart disease, aged 68. Graduate of Western Reserve University School of Medicine, Cleveland, 1935. Licensed in California in 1936. Dr. Knott was a retired member of the Los Angeles County Medical Association.

LACKNER, LOUIS, San Jose. Died July 21, 1977 in San Jose, aged 75. Graduate of the University of Colorado School of Medicine, Denver, 1925. Licensed in California in 1926. Dr. Lackner was a retired member of the Santa Clara County Medical Society.

LEVINSON, HERMAN, Bakersfield. Died June 23, 1977 in Bakersfield of cancer, aged 62. Graduate of Vanderbilt University School of Medicine, Nashville, 1939. Licensed in California in 1946. Dr. Levinson was a member of the Kern County Medical Society.

MEHERIN, JOSEPH MINTON, San Francisco. Died June 21, 1977 in San Francisco, aged 78. Graduate of Harvard Medical School, Boston, 1922. Licensed in California in 1923. Dr. Meherin was a member of the San Francisco Medical Society.

MORGAN, JOHN DANIEL, JR., Fresno. Died June 7, 1977 in Fresno, aged 87. Graduate of Vanderbilt University School of Medicine, Nashville, 1913. Licensed in California in 1913. Dr. Morgan was a retired member of the Fresno-Madera Medical Society.

MOSHOS, DON CARLOS, Torrance. Died December 27, 1976 in Loma Linda of hepatic coma, aged 66. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1944. Licensed in California in 1944. Dr. Moshos was a retired member of the Los Angeles County Medical Association.

MUNTER, EDGAR J., San Francisco. Died June 2, 1977 in San Francisco, aged 75. Graduate of the University of California Medical School, Berkeley-San Francisco, 1926. Licensed in California in 1926. Dr. Munter was a member of the San Francisco Medical Society.

NORBERG, RAYMOND WILLIAM, Whittier. Died January 26, 1977 in Laguna Hills of carcinoma of the stomach, aged 73. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1933. Licensed in California in 1933. Dr. Norberg was a retired member of the Los Angeles County Medical Association.

PLUMB, CHARLES E., St. Helena. Died November 14, 1976 of carcinoma of the colon, aged 85. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1927. Licensed in California in 1927. Dr. Plumb was a retired member of the Butte-Glenn Medical Society.

PORTNEY, GERALD LEE, Davis. Died May 23, 1977 in Sacramento following a splenectomy operation, aged 39. Graduate of Northwestern University Medical School, Chicago, 1962. Licensed in California in 1966. Dr. Portney was a member of the Yolo County Medical Society.

REISS, THOMAS HUBERT, Alameda. Died May 28, 1977 in Alameda of lymphoma, aged 78. Graduate of the University of California Medical School, Berkeley-San Francisco, 1926. Licensed in California in 1926. Dr. Reiss was a retired member of the Alameda-Contra Costa Medical Association.

SLOAN, JULIUS, Inglewood. Died May 19, 1977 in Culver City of acute myocardial infarction, aged 76. Graduate of the University of Minnesota Medical School, Minneapolis, 1934. Licensed in California in 1944. Dr. Sloan was a member of the Los Angeles County Medical Association.

SMITH, WILLIAM BURGETT, San Rafael. Died July 16, 1977 in Carmel of heart disease, aged 62. Graduate of the University of Chicago, The School of Medicine, 1940. Licensed in California in 1946. Dr. Smith was a member of the Marin Medical Society.

STAUB, JOHN SAMUEL, San Jose. Died June 1, 1977 in Palo Alto, aged 92. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1915. Licensed in California in 1916. Dr. Staub was a retired member of the Santa Clara County Medical Society.

STOUT, JOSEPH H., JR., Pasadena. Died June 2, 1977 in Pasadena, aged 69. Graduate of McGill University Faculty of Medicine, Montreal, 1940. Licensed in California in 1941. Dr. Stout was a member of the Los Angeles County Medical Association.

WALTERS, JOSEPH D., Sherman Oaks. Died April 26, 1977 in Sherman Oaks of heart disease, aged 74. Graduate of the Ohio State University College of Medicine, Columbus, 1931. Licensed in California in 1940. Dr. Walters was a member of the Los Angeles County Medical Association.

WEHRLY, MILDRED F., Palm Desert. Died July 4, 1977 in Fallbrook, aged 75. Graduate of the University of Southern California School of Medicine, Los Angeles, 1945. Licensed in California in 1945. Dr. Wehrly was a retired member of the Orange County Medical Association.

WINTER, ROBERT C., Manteca. Died May 30, 1977 in Manteca, aged 62. Graduate of the University of Nebraska College of Medicine, Omaha, 1939. Licensed in California in 1940. Dr. Winter was a member of the San Joaquin County Medical Society.

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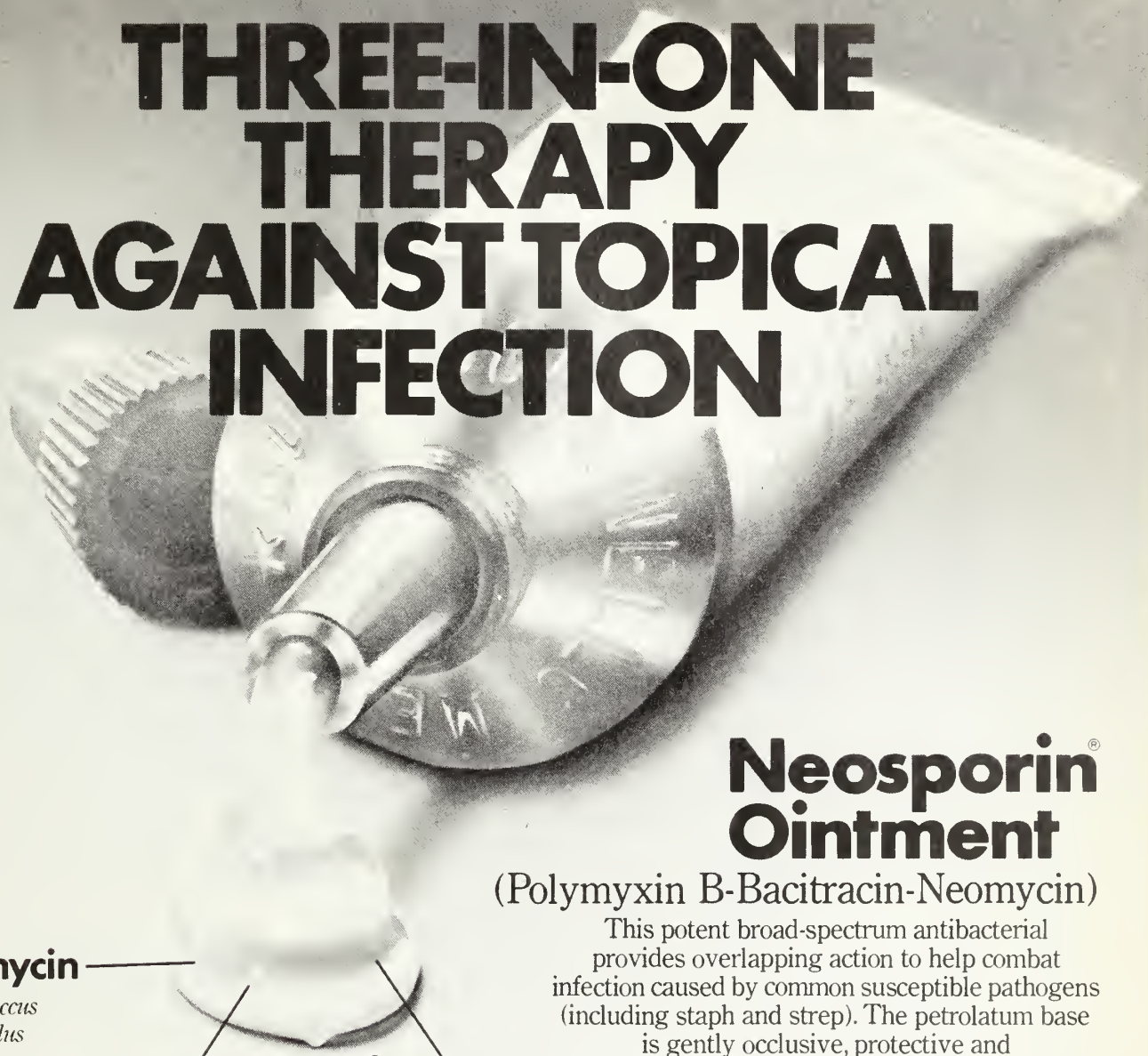

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(Continued on Page 26)

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NEW DEPARTMENT OF EMERGENCY MEDICINE, at UCSD Medical Center has openings for five certified specialists interested and experienced in emergency room medical care. Must be able and willing to supervise and teach house staff and medical students as well as be competent clinicians. Interest in clinical research in emergency medicine and working knowledge of Spanish language useful assets. California license required. Salary and clinical appointments of UCSD Medical Faculty commensurate with training and experience. Malpractice insurance and many fringe benefits included. UCSD is an equal opportunity/affirmative action employer. Send curriculum vitae to Hugh A. Frank, MD, Director of Emergency Services, 225 West Dickinson, San Diego, CA 92103.

CALIFORNIA, SAN JOSE: Experienced, career-oriented Emergency Physicians wanted to join well-established group practicing at a university affiliated hospital and a large community hospital. Beautiful San Francisco Bay area location. Fee-for-service compensation. ACEP preferred. Contact: James B. Lane, MD at (408) 293-8881 or write: 1530 The Alameda, No. 28, San Jose, CA 95126.

INTERNIST: BOARD CERTIFIED OR ELIGIBLE. Special training in chest diseases preferred but not required. Join a 19-MD multispecialty group located on the San Francisco peninsula. Hospital across the street and near 2 university hospital centers. Quality housing, schools and recreation; competitive starting salary with early progression to full partnership. Send curriculum vitae to or telephone Ronald L. Schwartz, Administrator, San Mateo Medical Clinic, 23 Baldwin Avenue, San Mateo, CA 94401. Phone (415) 342-7771.

MEDICAL EQUIPMENT FOR SALE

BENNET X-RAY UNIT—300MA 125 KV (Transistorized) Rotating Anode Tube (Dynamax 25-40) with Collimator Table with Bucky (No fluoro.). Complete dark room equipment, etc. Has been in daily use for chests, extremities and spines. Major components 3½ years old. ($3,500.00) Burdick Phomotograph FM-1 with chair ($35.00) Harry E. Fightlin, MD, Chartered, 318 Maryland Parkway, Las Vegas, Nevada 89101, Telephone (702) 382-3588.

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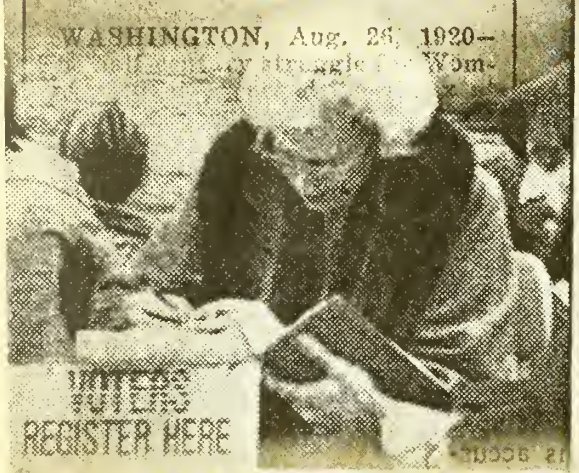
WASHINGTON, Aug. 26, 1920—



Social Security Bill Is Signed, Gives Pensions to Aged, Job

Roosevelt Approves Message Intended to Benefit 30,0 Persons When States Adopt Cooperating Laws—He the Measure 'Cornerstone' of His Economic Progr

WASHINGTON, Aug. 1 The Social Security Bill, p a broad program of unem insurance and old age and counted upon to ben 20,000,000 persons, becam day when it was signed b dent Roosevelt in the pre those chiefly responsible ting it through Co

Mr. Roosevelt cal "the cor erstone which is being me s c ple ri to

SENATE APPROVES 18-YEAR OLD VOTE IN ALL ELECTIONS

Amendment to Constitution is Sent to House, Where Passage is Expected

WASHINGTON, March 10, 1971—The Senate approved today 94 to 0, and sent to

TRUMAN CLOSES ITED NATIONS CONFEREN WITH PLEA TO TRANSLATE CHARTER INTO DEEDS

NEW WORLD HOPE

President Hails 'Great Instrument of Peace,' Insists It Be Used

HISTORIC LANDMARK

Meeting Gives Standing Ovation as Executive Pictures Peace Gain

"If we fail to use it," he declared to the solemn final meeting of the delegates, 'we shall betray all of those who have died in order that we might meet here in freedom and safety to create it.'

"If we seek to use it selfishly—for the advantage of any one nation or any small group of nations—we shall be equally guilty of that betrayal."

Fervent Interpolation

The President, speaking in the auditorium of the War Memorial Opera House, built in memory of sons of the Golden Gate city who gave their lives in the first World War, in which he himself served, seemed to give unconscious expression to the solemn feeling of the occasion when, at the outset of his speech, he interpolated the words, half a hope, half a prayer:

"Oh, what a great day this can be in history!"

Just before the plenary session the President accompanied the

JOL SIGN the Draf Ends No

WASHINGTON, Jan. 27, 1973—"With the signing of the peace agreement in Paris today, and after receiving a report from the Secretary of the Army that

PATIENT PACKAGE INSERTS: A CONCEPT WHOSE TIME HAS COME?

The consumer's right to know is an irreversible and desirable trend of the Seventies. It extends, and properly, to a patient's right to know more about his or her prescription medications. One way, gaining favor, is through patient package inserts. Wisely-prepared and properly distributed when medically indicated, they could markedly improve patient knowledge and drug therapy—laudable goals by anyone's standards.

The PMA endorses these goals and will work with government, the health professions and consumers to achieve them.

The Advantages

The concept holds promise of benefits: better patient understanding of the product prescribed, better adherence to the treatment plan, and more awareness of possible side reactions.

Every doctor has had patients who fail to finish antibiotic regimens because they feel better. Some patients assume that if one tranquilizer or analgesic is good, two may be twice as good. Still others fail to report dizziness while on antihypertensive therapy —and so on.

Problems like these might arise less often if the patient received written information in addition to verbal instructions. Some studies suggest that patients are more receptive to such materials, and they more often understand the verbal instructions and follow them, when inserts are used.

The Disadvantages

There are also some potential problems. Obviously, the inserts must be clearly phrased, without extraneous or complex detail. How much information is enough? How can it be kept current? Should all patients receive the same information? Should inserts be included with all drugs? Should only potential problems be listed or are patients better off with a "fair balance" presentation that describes usefulness as well as drawbacks?

These and similar questions require answers, since model inserts have yet to be properly developed and tested. Despite the need for these studies, the FDA is proceeding prematurely with inserts on selected products. We think the Congress is the only place where the matter can be given the proper legal status and direction, particularly since it represents a conceptual change in the legal, medical and social framework of the nation's prescription drug information system.

The Solution

The PMA believes that carefully-devised pilot studies of various kinds of inserts are needed. They should be developed and implemented with full participation by doctors, pharmacists, consumers, communications experts and the drug industry. Such studies will provide reliable pathways to follow, so that inserts will be useful aids to medical practice.

And particularly we think that you should be closely involved in this debate and in these studies and decisions. Otherwise, people with less experience and qualifications may control the purposes, content and use of a tool with considerable promise for improved patient care. It could make a difference in your practice tomorrow, and more importantly, in the health of your patients.

PMA
THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION
1155 FIFTEENTH ST, N W, WASHINGTON, D C 20005

(Continued from Page 23)

SITUATIONS WANTED

CARDIOLOGIST, university trained in non-invasive and invasive cardiology, seeks solo or group. Expertise in Sones and Judkins techniques. Interest in echo, stress testing, and permanent placement of pacemakers. Available Fall, 1977. Box 5946, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PHYSICIANS ASSISTANT, 1½ years experience in general practice, nationally certified, California license, seeks position with family practice or clinic. Contact Martin Solov, 3445 Colonial Drive, Apt. 107, Modesto, CA 95350.

PATHOLOGIST—Experienced AP-CP seeking a six months on/six months off position, ideally in alternation with solo incumbent tired of the grind. Prefer small city West or Southwest. Write Box No. 5947, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

HELP FOR STUDENT

U.C. GRADUATE seeks a loan for medical school. Terms negotiable. References available. Write Box No. 5948, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

OFFICES TO LEASE OR RENT

MEDICAL DENTAL UNIT for rent. Available in 2 months. Will remodel to suit. B Berger, MD, 1063 San Pablo, Pinole, CA 94564, (415) 758-2511.

CALIFORNIA—Glendale downtown, excellent location, single story beautiful Medical-Dental building, share office with dentist. Available 3 examination rooms, private office, lab. etc. $450. per month. Call (213) 221-6090. Joseph G. Goei, D.D.S., 3331 No. Broadway, Los Angeles, CA 90031.

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The 28-bed Kwajalein Hospital is modern and recently enlarged, and has a fully equipped outpatient clinic to handle the large flow of outpatients, plus excellent laboratory and X-ray facilities.

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Interested persons should RUSH curriculum vitae to: Clyde E. Albert, Global Associates, P.O. Box 12156, Oakland, California 94604.

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CANCER

September 17—**Clinical Implications of New Diagnostic Techniques—Ultrasound, Cat Scan, Radioisotopes, Clinical Chemistry.** San Francisco Regional Cancer Foundation at Fireman Fund Building, San Francisco. Saturday. 4 hrs. Contact: Norma Schlager, PhD, S.F. Regional Cancer Foundation, 14th and Lake, San Francisco 94118. (415) 221-2132.

October 3-7—**Medical Oncology Review.** American College of Physicians and Huntington Memorial Hospital at Huntington Sheraton Hotel, Pasadena. Monday-Friday. 36 hrs. $140, ACP members; $200, nonmembers. Contact: Arlene Ellis, Coord., Med. Staff Affairs, Huntington Mem. Hosp., 100 Congress St., Pasadena 91105. (213) 440-5176.

October 5—**Urological Cancer Conference—5th Annual.** L. A. Urological Society and American Cancer Society at Bonaventure Hotel, Los Angeles. Wednesday. 7 hrs. $60. Contact: Mari Hata, ACS, Calif. Division, 2932 Wilshire Blvd., Suite 202, Santa Monica 90403. (213) 828-7474.

November 18-19—**Endocrine Aspects of Cancer: New Perspectives.** Mt. Zion Hospital and Medical Center, San Francisco. Friday-Saturday. Contact: Ann Raisbeck, Dept. of Med. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2401.

December 3—**Physicians' Symposium on the Psychosocial Care of the Cancer Patient.** American Cancer Society, Alameda County Unit, at Claremont Hotel, Berkeley. Saturday. Contact: Robert Wooster, Ed. Dir., ACS, 1212 Broadway, Suite 612, Oakland 94602. (415) 832-7012.

January 27-28—**Cancer.** Peralta Hospital at Kaiser Center, Oakland. Friday-Saturday. Contact: Tish Hammerlee, Peralta Hosp., 450 30th St., Oakland 94609. (415) 451-4900, ext. 264.

January 30-31—**Cancer.** USC. Monday-Tuesday.

EMERGENCY MEDICINE

September 24—**Symposium on Pediatric Emergencies.** Children's Hosp. of L.A.; Hollywood Presbyterian Med. Ctr.; Emergent Care Cont. Ed. Ctr., Inc.; Emergency Dept. Physicians' Med. Grp., Inc. at Hollywood Presbyterian Medical Center. Saturday. 6½ hrs. $50. Contact: Philip J. Fagan, Jr., MD, Med. Dir., Emergency Dept. Physicians' Med Grp., Inc., 4640 Admiralty Way, Suite 508, Marina Del Rey 90291. (213) 822-1312.

September 25-30—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Town and Country Hotel, San Diego. Sunday-Friday.

September 26-30—**Topics in Emergency Medicine—Postgraduate Course for Career Emergency Physicians.** UCSF at Ralph K. Davies Medical Center, San Francisco. Monday-Friday. 40 hrs. $300.

October 5—**Symposium on Disaster Medicine.** UCLA aboard Queen Mary, Long Beach. Wednesday. 6 hrs. $15. Contact: Elton Blum, MD, L. B. City Health Dept., 2655 Pine Ave., Long Beach 90806.

October 24-28—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday.

November 8-10—**American College of Emergency Physicians—5th Annual Scientific Assembly.** Hilton Hotel, San Francisco. Tuesday-Thursday. 23 hrs. Contact: Meeting Registrar, ACEP, 3900 Capital City Blvd., Lansing, MI 48906. (517) 321-7911.

December 8-9—**Advances in Emergency Medicine—Metabolic Emergencies.** UCSF. Thursday-Friday.

December 12-16—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Islandia Hotel, San Diego. Monday-Friday.

January 23-27—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Town and Country Convention Center, San Diego. Monday-Friday. 40 hrs. $325.

January 23-27—**Topics in Emergency Medicine.** UCSF at Ralph K. Davies Medical Center, San Francisco. Monday-Friday.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

MEDICINE

September 20-November 8—**Current Practical Cardiology—1977.** Daniel Freeman Memorial Hospital, Inglewood. Tuesdays, 6:30-9:00 p.m. 16 hrs. $100 (includes dinner with each session). Contact: Donald A. Dennis, PhD, Dir. of Med. Ed., Daniel Freeman Memorial Hosp., 333 N. Prairie Ave., Inglewood 90301. (213) 674-7050, ext. 127.

September 26-30—**Medical Knowledge Self-Assessment Program Course.** American College of Physicians at Hilton Hotel, Los Angeles. Monday-Friday. 30 hrs. $140, ACP members; $200, nonmembers. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

September 29-30—**Annual Physician Postgraduate Symposium on Heart Disease.** San Francisco Heart Assn. and Council on Atherosclerosis, American Heart Assn., at Golden Gateway Holiday Inn, San Francisco. Thursday-Friday. Contact: Molly Austin, Assoc. Dir., S.F. Heart Assn., 421 Powell, San Francisco 94102. (415) 433-2273.

September 29-30 — **Clinical Immunology/Arthritis Update.** UCSF. Thursday-Friday. 13 hrs. $125.

October 1-8—**Cardiology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

October 3-7—**Medical Oncology Review.** See Cancer, October 3-7.

October 5—**Digitalis: New Insights at the Bicentennial.** L. A. Society of Internal Medicine at L.A. Co. Med. Assn., Los Angeles. Wednesday. 1½ hrs. $7.50 for dinner. Contact: Thomas T. Yoshikawa, MD, LASIM, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

October 5-6—**American Heart Association, Greater Los Angeles Affiliate—45th Annual Fall Symposium and 10th Annual Griffith Lecture.** Hilton Hotel, Los Angeles. Wednesday-Thursday. 12 hrs. $65, member of any Heart Assn.; $85, nonmember. Contact: LaVerna Titus, AHA, Greater L.A. Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

October 5-December 7—**Gastroenterology for the Practicing Internist.** UCLA. Wednesday evenings. $200.

October 6-7—**Pediatric Nephrology.** UCSF. Thursday-Friday.

October 7-8—**Practical Dermatopathology.** STAN at Holiday Inn, Palo Alto. Friday-Saturday. 16 hrs. $150; $100, residents and those in training. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Med. Ctr., Stanford 94305. (415) 497-6101.

October 8-15—**Endocrinology/Nephrology Review.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

October 10-14—**Practical Electro-Cardiography.** Memorial Hospital Medical Center of Long Beach-UCI at Hotel Inter-Continental, Maui, Hawaii. Monday-Friday. $150. Contact: Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 11-14—**Electrocardiography: Core Curriculum and Self-Assessment.** PMC at Golden Gateway Holiday Inn, San Francisco. Tuesday-Friday.

October 14—**Renal Disease—10th Annual Symposium.** Kidney Foundation of Northern Calif. at Hyatt on Union Square, San Francisco. Friday. $30, members; $35, non-members. Contact: Kidney Foundation of No. Calif., 100 S. Ellsworth, San Mateo. (415) 347-6646.

October 21-22—**Internal Medicine Symposium—22nd Annual.** Southern Calif. Permanente Medical Group at Hilton Hotel, Pasadena. Friday-Saturday. Contact: Shirley Gach, So. Calif. Permanente Med. Grp., 4900 Sunset Blvd., Rm. 6014, Los Angeles 90027. (213) 667-4241.

October 21-23—**Practical Cardiology—1977.** American College of Cardiology at Del Monte Hyatt Hotel, Monterey. Friday-Sunday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Division of Continuing Education, ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

October 26—**Consultations in Hypertensions.** UCSD at Vacation Village, San Diego. Wednesday.

October 28-29—**Diabetes.** STAN and Santa Clara County Diabetes Society at Palo Alto Medical Clinic. Friday-Saturday.

October 30-November 3—**American College of Chest Physicians—43rd Annual Scientific Assembly.** MGM Grand Hotel, Las Vegas. Sunday-Thursday. Contact: Dale E. Braddy, MS, Dir. of Education, ACCP, 911 Busse Highway, Park Ridge, IL 60068.

November 3-6—**California Society of Internal Medicine—Annual Meeting.** Canyon Hotel, Palm Springs. Thursday-Sunday. Contact: CSIM, 703 Market St., Suite 1412, San Francisco 94103. (415) 362-1548.

November 4-5—**Mechanisms of Hemostasis and Thrombosis: Experimental and Clinical Perspectives.** PMC at Fairmont Hotel, San Francisco. Friday-Saturday.

November 7-11—**Pediatric Allergy and Clinical Immunology.** UCSF. Monday-Friday.

November 7-16—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. 10 days. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Division of Continuing Education, ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

November 9—**Endocrinology Seminar.** LLU. Wednesday. 4 hrs. $25.

November 10-12—**Diagnosis and Management of Diseases of Peripheral Nerves and Muscle.** UCSD at Hilton Hotel, San Diego. Thursday-Saturday. 14 hrs. $125.

November 17-19—**Unusual Problems in Pulmonary Disease.** USC at Erawan Gardens, Palm Springs. Thursday-Saturday.

November 26-December 3—**Lymphoproliferative Disorders.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

December 2-4—**Advances in Heart Disease—1978.** American College of Cardiology at Fairmont Hotel, San Francisco. Friday-Sunday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Division of Continuing Education, ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

December 5-9—**Advances in Diagnosis and Treatment in Clinical Medicine.** American College of Physicians, Harbor General Hospital and St. Mary's Medical Center at Hyatt House Hotel, Los Angeles. Monday-Friday. Contact: Registrar, ACP, 4200 Pine St., Philadelphia, PA 19104.

December 7—**Current Data on the Epidemiology and Clinical Management of Essential Hypertension—Dinner Meeting/Scientific Program.** L. A. Soc. of Internal Medicine at L. A. County Medical Assn., Los Angeles. Wed. 1½ hrs. $7.50. Contact: Thomas T. Yoshikawa, MD, Prog. Chr., LASIM, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

December 10—**Pulmonary Artery Catheters and Ventilators.** PMC. Saturday. 6 hrs. $300.

December 12—**Current Concepts in Ileitis and Colitis.** UCD at Red Lion Motor Inn, Sacramento. Monday.

December 14—**Degenerative Diseases of the Aorta—3rd Annual Lyman A. Brewer III Cardiothoracic Symposium.** LLU at Century Plaza Hotel, Century City. Wednesday. 8 hrs. $50. Contact: Howard Whigham, PhD, Coor., Cont. Med. Ed., White Memorial Med. Ctr., 1720 Brooklyn Ave., Los Angeles 90033.

January 4-March 15—**Nights at UCLA: Infectious Diseases for the Practicing Internist.** Wednesdays; 7:30-9:30 p.m. 22 hrs. $200.

January 11—**Management of Arrhythmias.** LLU. Wednesday. 4 hrs. $25.

January 20-21—**Stress Testing: A New Look Forward to New Developments—Backward to Old Concepts.** American College of Cardiology at Memorial Hospital Medical Center, Long Beach. Friday-Saturday. Contact: Miss Mary Ann McInerny, Dir., Extramural Programs Dept., Div. of Cont. Ed., ACC, 911 Old Georgetown Rd., Bethesda, MD 20014.

January 21—**Systemic Disease/Eye, Mouth, Skin Manifestations.** See Of Interest to All, January 21.

January 24-27—**Present Concepts in Internal Medicine.** American College of Physicians at Letterman Army Medical Center, San Francisco. Tuesday-Friday. Contact: Registrar, ACP, 4200 Pine St., Philadelphia, PA 19104.

January 25-27—**Advances in Neurology.** UCSF at Hyatt on Union Square, San Francisco. Wednesday-Friday.

January 27-29—**New Frontiers on the Relationships of Lipids, Lipoproteins and the Arterial Wall in Cardiovascular Disease.** UC Extension, Berkeley, and UCSF at Hyatt on Union Square, San Francisco. Friday-Sunday. 12 hrs. $150. Contact: Medical Symposia, Div. of Letters and Sciences, UC Extension, Berkeley 94720. (415) 642-1061.

January 28—**Management of Fluid, Electrolyte and Acid-Base Disorders.** STAN. Saturday. 7 hrs.

February 15-17—**Recent Advances in Gastroenterology.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday.

February 23-25—**Cardiovascular Disease—1978: Practical Diagnosis and Management.** American College of Cardiology at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed. ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

OBSTETRICS AND GYNECOLOGY

September 30-October 1—**Office Gynecology Workshop.** PMC. Friday-Saturday.

October 12-16—**Pacific Coast Fertility Society—Annual Meeting.** Canyon Hotel, Palm Springs. Wednesday-Sunday. 21 hrs. $15, member; $25, nonmember. Contact: Ronald S. Swerdloff, MD, PCFS, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

October 17-21—**Obstetrics/Gynecology Review.** USC at Beverly Hilton Hotel, Beverly Hills. Monday-Friday.

October 28—**Advances in Obstetrics and Gynecology—11th Annual Meeting.** Northern Calif. Obstetrical and Gynecological Society at Red Lion Motor Inn, Sacramento. Friday. 7 hrs. Contact: Benjamin J. Berry, MD, Prog. Chr., NCOGS, 3720 Mission Ave., Carmichael 95608. (916) 481-5401.

November 10-12—**Menopause, Fetal Monitoring, and Genetics.** UCSF at Mark Hopkins Hotel, San Francisco. Thursday-Saturday.

November 12-14—**Comprehensive Laparoscopy: Current Principles and Practice.** UCSD at Kona Kai Club, Kona, Hawaii. Saturday-Monday.

November 12-19—**Endocrinology—Infertility.** UCSF at Kaui Surf, Kaui, Hawaii. One week.

January 14-21—**Perinatal Medicine.** USC at Royal Lahaina, Maui, Hawaii. One week.

January 28-30—**Comprehensive Laparoscopy.** UCSD at Kona Kai Club, San Diego. Saturday-Monday. 16 hrs. $375.

February 11-12—**Obstetrical and Gynecological Forum.** L. A. Obstetrical and Gynecological Society at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. Contact: Ms. Dee Davis, Exec. Sec., L. A. Obstetrical and Gynecological Society, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

PEDIATRICS

September 15-16—**Pediatric Urology.** See Surgery, September 15-16.

September 24—**Symposium on Pediatric Emergencies.** See Emergency Medicine, September 24.

September 28-29—**Brennemann Memorial Lectures—34th Annual.** L.A. Pediatric Society at Bonaventure Hotel, Los Angeles. Wednesday-Thursday. Contact: Eve Black, Exec. Sec., LAPS, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

A Symposium:

MECHANISMS OF HEMOSTASIS AND THROMBOSIS:

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Proceedings will be available in printed and taped form.

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PACIFIC MEDICAL CENTER
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SAN FRANCISCO, CA 94120
(415) 563-4321

Space is limited, so register early.

October 1—**Clinical Problems in Immunology—Annual Pediatric Seminar.** Permanente Medical Group, Oakland. Saturday. Contact: Stephen L. McMurtry, MD, Dept. of Ped. Kaiser Hospital, 975 Sereno Dr., Vallejo 94590.

October 6-7—**Pediatric Nephrology.** See Medicine, October 6-7

October 7-8—**Genetic Disorders for the Pediatrician.** Children' Hospital Medical Center, Oakland, at Highlands Inn, Carmel Friday-Saturday. Contact: Gretchen Hayes, CHMC, 51s and Grove Sts., Oakland 94609.

October 15-22—**Pediatrics for the Practitioner.** Children's Hospital of Long Beach and American Academy of Pediatrics Chapter 2, at Mauna Kea Beach Hotel, Kamuela, Hawai One week. Contact: Margaret Frederick, Exec. Sec., Cente for Health Education, 2801 Atlantic Ave., Long Beac 90801. (213) 595-3811.

October 21-22—**Adolescence Sexuality and Related Problem** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturda

November 4-5—**Children's Experiences of Health and Illnes** UCD at Claremont Hotel, Berkeley. Friday-Saturday.

November 7-11—**Pediatric Allergy and Clinical Immunolog** See Medicine, November 7-11.

December 3—**Practical Aspects of Sports Medicine for Pedi tricians.** American Academy of Pediatrics, Calif. Chapter Dist. IX, at Union Square Holiday Inn, San Francisco. Sa urday. Contact: Martin Gershman, MD, 595 Buckingha Way, San Francisco 94132.

January 12-14—**General Pediatrics.** American Academy of Pediatrics at Kona Surf Hotel, Kailua-Kona, Hawaii. Thursday-Saturday. Contact: L. J. Nagel, Dept. of Cont. Ed., AAP, P.O. Box 1034, Evanston, IL 60204. (312) 869-4255.

January 26-28—**Troubled Youth.** See Psychiatry, January 26-28.

January 27-29—**Pediatric Anesthesiology.** See Surgery and Anesthesiology, January 27-29.

February 10—**Pediatric Otolaryngology.** See Surgery and Anesthesiology, February 10.

PSYCHIATRY

September 23-24—**The Hysterical Personality.** UCD at Claremont Hotel, Berkeley. Friday-Saturday. 8 hrs. $85.

September 24-25—**Mind Altering Drugs in Clinical Practice.** UCLA. Saturday-Sunday. 14 hrs. $140.

October 1-2—**Stress Management and Approaches to Stress.** See Of Interest To All, October 1-2.

November 13-16—**Academy of Psychosomatic Medicine.** South Coast Plaza Hotel, Costa Mesa. Sunday-Wednesday. 22 hrs. Contact: Mark C. Lukas, APM, 4902 Tollview Dr., Rolling Meadows, IL 60008. (312) 398-3140.

November 14-18—**Group Therapy Seminars.** UCSF at Merritt Hotel, Oakland. Monday-Friday.

anuary 10-March 21—**Intensive Review of Psychiatry.** USC. Tuesday evenings.

anuary 20-22—**A Retrospective Psychoanalytically Oriented Psychotherapy.** UCSF. Friday-Sunday.

anuary 26-28—**Troubled Youth.** USC at Vacation Village, San Diego. Thursday-Saturday.

ebruary 8—**Psychiatry Seminar.** LLU. Wednesday. 4 hrs. $25.

ADIOLOGY AND PATHOLOGY

ptember 17—**Radiology Symposium—5th Annual.** Southern Calif. Permanente Medical Group at Bonaventure Hotel, Los Angeles. Saturday. Contact: Shirley Gach, So. Calif. Permanente Med. Grp., Education and Research Dept., 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

ptember 17—**Clinical Implications of New Diagnostic Techniques—Ultrasound, Cat Scan, Radioisotopes, Clinical Chemistry.** See Cancer, September 17.

tober 8-16—**Body Imaging Conference—2nd Annual.** West Park Hospital, Canoga Park, at Kauai Surf Hotel, Kauai, Hawaii. One week. 25 hrs. $295. Contact: Ronald J. Freidman, MD, Dept. of Radiology, West Park Hospital, 22414 Roscoe Blvd., Canoga Park 91304.

tober 21-23—**Society of Nuclear Medicine—2nd Annual Western Regional Meeting.** Aladdin Hotel, Las Vegas. Friday-Sunday. Contact: Justine J. Lynch, P.O. Box 40279, San Francisco 94140. (415) 647-0722 or (415) 647-5909.

uary 16-20—**Computed Tomography.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. $295.

uary 27-29—**Los Angeles Radiological Society—13th Annual Mid-Winter Meeting.** Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Nathan Green, MD, 15107 Vanowen St., Van Nuys 91405.

uary 27-29—**New Frontiers on the Relationships of Lipids, Lipoproteins and the Arterial Wall in Cardiovascular Disease.** See Medicine, January 27-29.

ruary 19-24—**Interpretative Enzymology.** UCSD at Sheraton Inn-Airport, San Diego. Sunday-Friday. 25 hrs.

tgraduate Videotape Programs in Diagnostic Radiology. eveloped by Dept. of Radiology, UCSF. 15 programs in all pects of diagnostic radiology. Outstanding group of nanal and international guest lecturers in addition to UC aff present basic approaches to radiographic interpretation d technique as well as new research and clinical advances. ntact: Aveleen Blumenstock, Videotape Coordinator, Dept. Radiology, UCSF, San Francisco 94143. (415) 666-1988.

Medical Symposia in San Francisco

presented by University of California Extension, Berkeley; cosponsored by Continuing Education, University of California School of Medicine, San Francisco

Clinical Toxicology, Pharmacology, and Carcinogenic Hazards

December 9-11, 1977

Updated information on drug toxicology, clinical pharmacology, and environmental pollutants as well as carcinogenic hazards of drugs and chemicals. Highlighted will be new techniques for identifying drug overdose and monitoring therapeutically used drugs.

New Frontiers on the Relationships of Lipids, Lipoproteins, and the Arterial Wall in Cardiovascular Disease

January 27-29, 1978

Highlights testing for lipids and lipoproteins, classification of diseases associated with lipid abnormalities, and the importance of HDL in preventing artery disease.

CMA and AMA certification credit authorized for both symposia.

Detailed information: call (415) 642-1061; or write Dept. SC, Division of Letters and Sciences, University of California Extension, Berkeley, CA 94720.

SURGERY AND ANESTHESIOLOGY

September 15-16—**Pediatric Urology.** UCD at Hyatt Lake Tahoe. Thursday-Friday. 10 hrs. $150.

September 16-17—**Ophthalmology Update III.** PMC at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. 13 hrs. $225.

October 5—**Urological Cancer Conference.** See Cancer, October 5.

October 10-14—**Congress of Neurological Surgeons.** Hilton Hotel, San Francisco. Monday-Friday. 40 hrs. $75, members; $100, nonmembers. Contact: David L. Kelly, Jr., MD, Bowman Gray School of Medicine, Winston-Salem, NC 27103. (919) 727-4653.

October 12-16—**Pacific Coast Fertility Society—Annual Meeting.** See Obstetrics and Gynecology, October 12-16.

October 14—**Renal Disease—10th Annual Symposium.** See Medicine, October 14.

October 21-22—**Trauma: Immediate Care.** UCSF. Friday-Saturday.

October 23-November 4—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200 for otolaryngologists; $900, residents. Contact: Malcolm D. Graham, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

October 28-29—**The Macula.** Retina Research Fund of St. Mary's Hospital and Medical Center at Hyatt on Union Square, San Francisco. Friday-Saturday. Contact: Claire Ohiyon, c/o Howard Schatz, MD, 3637 Sacramento St., San Francisco 94118. (415) 921-4860.

October 30-November 4—**American Society of Plastic and Reconstructive Surgeons—Annual Convention.** Hilton Hotel, San Francisco. Sunday-Friday. 33 hrs. Contact: Linda Campbell, ASPRS, 29 E. Madison St., Chicago 60602. (312) 641-0593.

Novemper 3-5—**Nerve Repair: Clinical and Experimental Basis.** UCSF. Thursday-Saturday.

November 5—**Review of Retinal Disease and Surgery.** The Retina Research Fund of St. Mary's Hospital at Hyatt on Union Square, San Francisco. Saturday. 7 hrs. Contact: Howard Schatz, MD, 3637 Sacramento St., San Francisco 94118.

November 12—**Current Concepts in Ophthalmic Plastic Surgery.** Jules Stein Eye Institute, Los Angeles. Saturday. Contact: Shelley E. Reid, Jules Stein Eye Institute, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

November 17-18—**Legg-Calve-Perthes Symposium.** Orthopaedic Hospital, Los Angeles, at Airport Park Hotel, Inglewood. Thursday-Friday. $200. Contact: Med. Ed. Dept., Orthopaedic Hospital, 2400 S. Flower St., Los Angeles 90007.

November 18-19—**Strabismus.** PMC. Friday-Saturday. 16 hrs.

November 19-20—**American Society of Anesthesiologists—Regional Refresher Course.** Sahara Hotel, Lake Tahoe. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

November 30-December 1—**Annual Ophthalmology Program.** UCSF. Wednesday-Thursday.

November 30-December 3—**Applied Biomechanics for Orthopedic Surgeons.** UCLA. Wednesday-Saturday. 23 hrs. $200.

December 2-4—**ENG Workshop.** PMC at Ilikai Hotel, Honolulu. Friday-Saturday. 24 hrs. $395.

December 3—**Emergency Anesthesia.** Sacramento Valley Anesthesia Society; UCD; Calif. Society of Anesthesiologists at Red Lion Motor Inn, Sacramento. Saturday. $50. Contact: John H. Eisele, MD, Dept. of Anesthesiology. UCD Sch. of Med., Davis 95616. (916) 752-2703.

December 14—**Treatment of Parkinsonism and Modern Concepts.** LLU. Wednesday. 4 hrs. $25.

January 5-7—**Anesthesia Update '78.** UCSD at Hotel Del Coronado, Coronado. Thursday-Saturday. 15 hrs. $150.

January 16-20—**Otologic Surgery—13th Annual Course.** Ear Research Institute, Los Angeles. Monday-Friday. 45 hrs $500. Contact: F. H. Linthicum, Jr., MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

January 22-26—**Ophthalmology and Otolaryngology—47th Annual Mid-Winter Clinical Convention.** The Research Study Club of Los Angeles, Inc., at Hilton Hotel, Los Angeles. Sunday-Thursday. 28 hrs. $175. Contact: Mr. Richard Pruter, Exec. Sec., P. O. Box 49412, Los Angeles 90049 (213) 879-0143.

January 27-29—**Pediatric Anesthesiology—16th Clinical Conference.** Children's Hospital of Los Angeles at Marriot Hotel, Los Angeles. Friday-Sunday. 15 hrs. $135. Contact Wayne Herbert, MD, Children's Hosp., 4650 Sunset Blvd. Los Angeles 90027. (213) 660-2450, ext. 2262.

February 10—**Pediatric Otolaryngology.** USC. Friday.

February 28-March 3—**Diagnosis and Management of Acoustic Neuromas and Skull Base Tumors.** Ear Research Institute Los Angeles. Tuesday-Friday. 32 hrs. $400. Contact: William F. House, MD, Ear Research Institute, 256 S. Lake St. Los Angeles 90057. (213) 483-4431.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213 682-1760.

OF INTEREST TO ALL PHYSICIANS

September 15-April 20—**Differential Diagnosis.** USC. Thursda evenings.

September 24-25—**Mind Altering Drugs in Clinical Practice.** Se Psychiatry, September 24-25.

September 24-25—**National Symposium on Patient Educatio** UCSF; American Hosp. Assn.; National Bureau for Healt Education; National Center for Health Education, Inc Society for Public Health Education, No. Calif. Chapte Stanford Univ. Hospital at UCSF. Saturday-Sunday. $65.

September 25-28—**Physical Fitness Seminar.** LLU at Muriett Hot Springs. Sunday-Wednesday. 8½ hrs. Contact: Alumr Assn., LLU Sch. of Med., Loma Linda 92354. (714) 79 7311, ext 2389.

September 30-October 2—**Society of Prospective Medicin** Society of Prospective Medicine, San Diego State Univ Methodist Hosp. of Indianapolis, and UCSD at Bahia Mot Hotel, San Diego. Friday-Sunday. 20 hrs. Contact: Charl M. Ross, MD, Society of Prospective Medicine, 2970 5t Ave., San Diego 92103.

October 1-2—**Practical Nephrology for the Primary Care Phys cian.** UCLA. Saturday-Sunday.

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October 1-2—**Stress Management and Approaches to Stress.** UCSF at Sheraton Palace Hotel, San Francisco. Saturday-Sunday.

October 3-7—**Primary Care.** STAN. Monday-Friday.

October 5—**Digitalis: New Insights at the Bicentennial—Dinner Meeting/Scientific Program.** L. A. Society of Internal Medicine at L. A. County Med. Assn., Los Angeles. Wednesday. 1½ hrs. $7.50. Contact: Thomas T. Yoshikawa, MD, LASIM, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

October 5—**Symposium on Disaster Medicine.** See Emergency Medicine, October 5.

October 5-9—**Pharmacology—Rational Basis of Therapeutics.** UCSF at Hilo, Hawaii. Wednesday-Saturday. $225.

October 6-8—**Western Occupational Health Conference—21st Annual.** Western Occupational Medical Assn. at Fairmont Hotel, San Francisco. Thursday-Saturday. Contact: B. H. Bravinder, Exec. Sec., WOMA, P.O. Box 201, Alamo 94507. (415) 837-0874.

October 7-9—**Lesbians and Gay Men: Clinical and Cultural Perspectives.** UCSF Human Sexuality Program. Friday-Sunday. 26 hrs. $85. Contact: Human Sexuality Program, 350 Parnassus, Suite 700, San Francisco 94143. (415) 666-4787.

October 8—**Hormones and Sexuality, Part I.** UCLA. Saturday. $65 for both parts; $35, one part.

October 10-13—**American Academy of Family Physicians.** Hilton Hotel, Las Vegas. Monday-Thursday. Contact: AAFP, 1740 W. 92nd St., Kansas City, MO 64114.

October 11-16—**Society for Clinical and Experimental Hypnosis—29th Annual Workshops and Scientific Meeting.** Hyatt House, Los Angeles. Tuesday-Sunday. 30 hrs. Contact: Marion Kenn, SCEH, 129-A Kings Park Dr., Liverpool, NY 13088. (315) 652-7299.

October 12—**Pain and Its Management.** LLU. Wednesday. 4 hrs. $25.

October 12-16—**Pacific Coast Fertility Society.** See Obstetrics and Gynecology, October 12-16.

October 14-15—**Neurology for the Non-Neurologist.** Mt. Zion Hospital and Medical Center, San Francisco. Friday-Saturday. Contact: Ann Raisbeck, Dept. of Med. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2401.

October 14-16, 21-23—**Introduction to Sex Counseling Principles.** UCSF Human Sexuality Program at UCSF. Two weekends. 50 hrs. $175, per person; $300, per couple. Contact: Susan Hansen, Human Sexuality Program, 350 Parnassus, Suite 700, San Francisco 94143. (415) 666-4787.

October 15, 19, 26, November 2, 9—**Caring for the Patient as a Human Being.** UC Extension, Berkeley, and Institute for the Study of Humanistic Medicine at UC Extension Center, San Francisco. Saturday and four Wednesday afternoons. Contact: Letters and Sciences, UC Extension, 2223 Fulton St., Berkeley 94720. (415) 642-1061.

October 17-21—**Family Practice Review—2nd Annual.** LLU. Monday-Friday. 30 hrs. $150.

October 22—**Selected Topics on Infectious Disease.** PMC. Saturday. 6 hrs. $80.

October 27-28—**Living with Chronic and Terminal Illness.** PMC. Thursday-Friday. 6 hrs. $60.

October 29—**Audiology Update for Primary Care Physicians.** PMC. Saturday. 6 hrs. $80.

October 29—**Hormones and Sexuality, Part II.** UCLA. Saturday. $65 for both parts; $35, one part.

October 30-November 3—**American Medical Association—Regional Meeting.** Sheraton Waikiki, Honolulu, Hawaii. Sunday-Thursday. Contact: AMA, 535 N. Dearborn, Chicago 0610.

TWENTY-FIRST ANNUAL

WESTERN OCCUPATIONAL HEALTH CONFERENCE

Fairmont Hotel—San Francisco

OCTOBER 6, 7, 8—1977

"Carcinogens, Mutagens and Teratogens: Some Delayed Effects of the Occupational Environment"

THURSDAY, OCTOBER 6—1:00 p.m.-4:30 p.m.

WOMA POSTGRADUATE SEMINAR

STRESS, DISTRESS AND HARASSMENT
J. S. FELTON, MD, FAOMA, moderator, Naval Regional Medical Center, Long Beach, CA

THE VIEWPOINT OF THE PRIMARY PHYSICIAN
JOSEPH LaDOU, MD, FAOMA, Peninsula Industrial Medical Clinic, Sunnyvale, CA

THE VIEWPOINT OF THE GASTROENTEROLOGIST
HOWARD SHAPIRO, MD, FACP, University of California, San Francisco, CA

THE VIEWPOINT OF THE CARDIOLOGIST
EUGENE P. SHAFTON, MD, FACC, University of California, San Francisco, CA

THE VIEWPOINT OF THE PSYCHIATRIST
DANIEL CHAFFIN, MD, FAPA, University of California, San Francisco, CA

FRIDAY, OCTOBER 7—Morning

GENERAL SESSION

CARCINOGENS, MUTAGENS AND TERATOGENS: Some Delayed Effects of the Work Environment

WELCOME
WILLIAM B. WHITING, MD, FAOMA, State Compensation Insurance Fund, San Francisco, CA, General Conference Chairman

KEYNOTE ADDRESS NUMBER 1
OCCUPATIONAL HEALTH AS A TEAM EFFORT: THE CHALLENGE OF ENVIRONMENTAL CARCINOGENS
EULA BINGHAM, PhD, Assistant Secretary of Labor for Occupational Safety and Health Administration (OSHA)

KEYNOTE ADDRESS NUMBER 2
LEGISLATIVE RESPONSIBILITY
ARLEN GREGORIO, California State Senator, Tenth District, Chairman of the State Senate Health and Welfare Committee

Afternoon

PANEL DISCUSSION AND OPEN FORUM
NEW DEVELOPMENTS
AUSTIN E. GIVENS, MD, FAOMA, moderator, E. I. DuPont de Nemours, Antioch, CA

SCIENTIFIC JUDGMENT AND ZERO CONCEPT
HAROLD HODGE, PhD, ScD, University of California, San Francisco, CA

ENVIRONMENTAL MUTAGENS/CARCINOGENS AND THEIR DETECTION
BRUCE AMES, PhD, University of California, Berkeley, CA

PANEL DISCUSSION AND OPEN FORUM
PREVENTION AND CONTROL
REYNOLD T. SCHMIDT, MD, FAOMA, moderator, Union Oil Company of California, Los Angeles, CA

THE VIEWPOINT OF THE PHYSICIAN
DAVID P. DISCHER, MD, FAOMA, San Jose Medical Clinic

THE VIEWPOINT OF THE ENVIRONMENTAL TOXICOLOGIST
NICK PROCTOR, PhD, Kaiser Aluminum and Chemical Corporation, Oakland, CA

THE VIEWPOINT OF THE HEALTH PHYSICIST
ROLAND FINSTON, PhD, Stanford University Medical Center, Stanford, CA

THE VIEWPOINT OF THE OCCUPATIONAL HEALTH NURSE
JOYCE SIMONOWITZ, RN, COHN, State Department of Health, Los Angeles, CA

SATURDAY, OCTOBER 8

GENERAL SESSION

THE UNBORN CHILD AND THE WORK PLACE
PIERO MUSTACCHI, MD, FCAP, moderator, University of California, San Francisco, CA

TERATOGENESIS: ITS IMPACT ON THE FERTILE WORKING WOMAN
ANN M. WOLVEN, Syntex Corporation, Palo Alto, CA

LEGAL PERSPECTIVES

THE LAW AND FAIR EMPLOYMENT PRACTICES
KATHLEEN MURRAY, JD—Legal Counsel, Fair Employment Practice Commission, San Francisco, CA

LEGAL LIABILITY AND LIMITATIONS
KATHRYN E. RINGGOLD, JD—Attorney at Law, Airola and Ringgold, San Francisco, CA

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SESSIONS TAPED—Sessions will be professionally taped and the cassettes will be on sale.

MESSAGE CENTER—Courtesy of Pacific Telephone—(415) 781-4300 is provided for your message use during the conference.

Contact **B. H. BRAVINDER, Ex. Sec., Box 201, Alamo, Calif. 94507 Phone (415) 837-0874** for pre-registration information.

October 31-November 4—**Intensive Care.** STAN. Monday-Friday.

November 5—**Current Concepts of Gonococcal Disease—Dinner Meeting/Scientific Program.** L. A. Society of Internal Medicine at L. A. County Med. Assn., Los Angeles. Saturday. 1½ hrs. $7.50. Contact: Thomas T. Yoshikawa, MD, LASIM, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

November 5-6—**Practical Rheumatology for the Primary Care Physician.** UCLA and Arthritis Foundation, Southern California Chapter, at UCLA. Saturday-Sunday. 12 hrs. $145.

November 6-8—**Dermatology for the Family Practitioner.** UCD at Del Monte Hyatt House, Monterey. Sunday-Tuesday. 14½ hrs. $100.

November 6-9—**California Academy of Family Physicians—Annual Scientific Assembly.** Masonic Auditorium, San Francisco. Sunday-Wednesday. Contact: CAFP, 9 First St., San Francisco 94105. (415) 982-6091.

November 11-13—**Health Aspects of Human Sexuality.** UCSF Human Sexuality Program. Friday-Sunday. 20 hrs. Contact: Human Sexuality Program, 350 Parnassus, Suite 700, San Francisco 94143. (415) 666-4787.

November 18-20—**Sexual Problems in Medical Practice.** USC at Gene Autry Hotel, Palm Springs. Friday-Sunday.

December 1-3—**Human Sexuality.** UCD at Hyatt Lake Tahoe, Incline Village. Thursday-Saturday.

December 5-9—**Advances in Diagnosis and Treatment in Clinical Medicine.** See Medicine, December 5-9.

December 9-11—**Clinical Toxicology, Pharmacology and Carcinogenic Hazards.** UC Extension, Berkeley, and UCSF at Hyatt Regency Hotel, San Francisco. Friday-Sunday. 13 hrs. $150. Contact: Medical Symposia, Div. of Letters and Sciences, UC Extension, Berkeley 94720. (415) 642-1061.

December 14—**Treatment of Parkinsonism.** See Surgery, December 14.

January 18-20—**Infectious Disease.** USC. Wednesday-Friday.

January 19-21—**Medical Aspects of Aging.** UCLA at Valley Hilton Hotel, Sherman Oaks. Thursday-Saturday.

January 21—**Systemic Disease/Eye, Mouth, Skin Manifestations.** Continuing Medical Education/San Luis Obispo Consortium at Hilton Inn, San Luis Obispo. Saturday. 5 hrs. $25 for non-consortium members. Contact: Billy Mounts, MD, Chr., CME/SLO Consortium, P.O. Box 319, San Luis Obispo 93406.

January 23-27—**Therapy: Principles and Use of Drugs.** STAN. Monday-Friday. 27 hrs. $265.

January 27-28—**Nutrition.** UCSF. Friday-Saturday.

January 28-29—**Pediatric Update for Family Practitioners.** UCLA. Saturday-Sunday. 10 hrs. $135.

February 1-4—**Physician and the Hospital.** USC at Canyon Hotel, Palm Springs. Wednesday-Saturday.

February 8-11—**Primary Care—Current Management of Common Office Problems.** UCSF. Wednesday-Saturday.

February 10-11—**Alcoholism Update—4th National Seminar.** Vista Hill Foundation at Hotel del Coronado, Coronado. Friday-Saturday. 9 hrs. Contact: Virginia Everett, Dir., Public Relations, Vista Hill Foundation, 7798 Starling Dr., San Diego 92123. (714) 278-6761.

February 10-12—**Headaches: Evaluation and Management.** UCLA at Beverly Hilton Hotel, Beverly Hills. Friday-Sunday. 18 hrs.

February 15-17—**Course for Physicians in Family Practice—27th Annual.** Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Ann Raisbeck, Dept. of Med. Ed., Mt. Zion Hospital and Med. Ctr., P. O. Box 7921, San Francisco 94120. (415) 567-6600, ext 2401.

February 20-24—**Caring for Older Persons.** Medical Communications and Services Assn. at Kona Surf Hotel, Kailua, Kona, Hawaii. Monday-Friday. 31 hrs. $195. Contact: MCSA, 315 University District Bldg., 1107 N. E. 45th St., Seattle, WA 98105. (206) 633-0505.

February 27-March 3—**Basic Science for Clinicians.** STAN. Monday-Friday. 24½ hrs. $265.

February 27-March 3—**Clinical Management of Sexual Problems.** Medical Communications and Services Assn. at Sheraton Hotel, Molokai, Hawaii. Monday-Friday. 30 hrs. $195. Contact: MCSA, 315 University District Bldg., 1107 N. E. 45th St., Seattle, WA 98105. (206) 633-0505.

Audio-Digest Foundation. A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $90 per year. Also available are ACOG Audio Education Courses, edited and produced by Audio-Digest Foundation—32, 6- and 3-hour cassette courses available including: Family Life and Sexual Counseling; Medical Complications of Pregnancy; Gynecological Endocrinology; Psychosomatic Ob/Gyn; Immunology in Ob/Gyn; and Pediatric and Adolescent Gyn. Available soon: Cassette albums of State of the Art Lectures and Workshops from 1976 American College of Physicians meeting and Postgraduate Courses from 1976 American Psychiatric Association meeting. Contact: Mr. Claron L. Oakley, Editor, 1577 E. Chevy Chase Dr., Glendale 91206.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU Four weeks or more, by arrangement. Bedside and classroon training, practical aspects of clinical care and management 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care LLU. Four weeks or more, by arrangement. Diagnostic anc therapeutic methods in medical chest disease, physiologica methodology of modern pulmonary care programs, use o: new instrumentation in the field. 160 hrs. Contact: John E Hodgkin, MD, Chief, Section of Medical Chest Diseases LLU.

Physician-in-Residence Preceptorship in Pulmonary Disease USC, Pulmonary Disease Section, Dept. of Medicine anc Postgraduate Medical Education. One month or more, b arrangement. Opportunity for practicing physician to achiev specified knowledge and skills in adult pulmonary medicine Contact: Oscar J. Balchum, MD, PhD, USC.

Training for Physicians in Nephrology. LLU. Four weeks o more, by arrangement. Hemodialysis, peritoneal dialysis renal biopsy, and kidney transplantation. 160 hrs. Contact Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 pe mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wedne days or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Period begin Oct., Jan., or April. $100. Contact: Harold M. Schneic man, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for fou weeks. To be arranged. $250. Contact: Rodney J. Valentin MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysic Dermatology, Echocardiography, International Health, M crobiology, Neurological Surgery, Obstetrics and Gynecolog Pediatrics, Pharmacology and Experimental Therapeutic Physiology, Psychiatry, Urology. UCSF. By special a rangement.

Traineeships in Renal Dialysis. UCSF. By special arrangemen

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Department of Internal Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen R. Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, 97201.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

October 20-21—**Seventeenth Annual Postgraduate Course in Medicine and Surgery.** Providence Hospital, Department of Family Practice, 700 NE 47th, Portland 97213. Contact: Robert Cockburn, MD, 9204 SE Mitchell, Portland 97266.

INTERNAL MEDICINE

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

September 16-17—**Recent Developments in the Management of Infectious Disease.** Rogue Valley Country Club, Medford. Contact: J. S. Reinschmidt, MD, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

October 9-12—**Workshop in Electrocardiography.** Hilton Hotel, Portland. Contact: Henry J. L. Marriott, MD, Box 14405, St. Petersburg, FL 33733.

November 2-4—**Oregon Medical Association Annual Scientific Session.** Red Lion Motor Inn and Oregon Medical Association Headquarters, Portland. Contact: Sondra Gleason, Oregon Medical Association, 5210 SW Corbett Street, Portland 97201.

November 4-5—**Fourth Annual Critical Care Symposium.** Sheraton Hotel, Portland. Contact: J. S. Reinschmidt, MD, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

November 8—**Oregon Lung Association Sixth Annual Respiratory Disease Conference.** Sacred Heart Hospital, Eugene. Contact: Oregon Lung Association, 1020 SW Taylor, Portland 97205.

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September 21—**Evaluation of Acute Trauma.** Univ. of Wash. in Anacortes, Wash. Wednesday, 8-10 a.m., Island Hospital. Contact: Harry Eiesland, MD, 24th St. and "M" Ave., Anacortes, WA 98221. (206) 293-3101.

September 21-23—**Renal Pathophysiology and Renal Failure—Univ. of Wash. Internal Medicine Review Sessions in Montana.** Wednesday, Sept. 21, Great Falls. Contact: Mr. John Breeden, Box 2829, Great Falls, MT 59403. (406) 453-1493. Thursday, Sept. 22, Billings; 7:30-10 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, Sept. 23, Missoula; 8:30-11 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

September 22-25—**Washington State Medical Association Annual Meeting.** Friday-Sunday. Washington Plaza Hotel, Seattle. Contact: Mr. Harlan Knudson, Exec. Dir., Washington State Medical Association, 900 United Airlines Bldg., Seattle, WA 98121. (206) 623-4801.

September 26-27—**Leukemia and Lung Cancer—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, Sept. 26, Wenatchee; 7:30-9:00 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, Sept. 27, Yakima: 5-7 p.m., Memorial Hospital. Contact: Harry Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 248-6791.

September 29-30—**Arthritis Foundation, Western Washington Chapter: Current Concepts in Arthritis.** Thursday-Friday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

September 29-October 1—**Montana Medical Association Annual Meeting.** Monday-Thursday. Village Motor Inn, Missoula, Mont. Contact: Mr. G. Brian Zins, Exec. Dir., Montana Medical Association, 2021 Eleventh Ave., Helena, MT 59601. (406) 443-4000.

October 4-7—**Antibiotics.** Tuesday-Friday. Tacoma General Hospital, Tacoma, Wash. 8 hrs. Fee to be determined. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

October 14-15—**Annual Cancer Conference.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

October 24-25—**Anaerobic Infections, Post-operative Infections, Infections of the Nervous System—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, Oct. 24, Wenatchee; 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, Oct. 25, Yakima, 5-7 p.m., Memorial Hospital. Contact: Harry Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 248-6791.

October 26-28—**Lipid Metabolism in Diabetes—Univ. of Wash. Internal Medicine Review Sessions in Montana.** Wednesday, Oct. 26, Great Falls. Contact: Mr. John Breeden, P.O. Box 2829, Great Falls, MT 59403. (406) 453-1493. Thursday, Oct. 27, Billings; 7:30-10 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, Oct. 28, Missoula; 8:30-11 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

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Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

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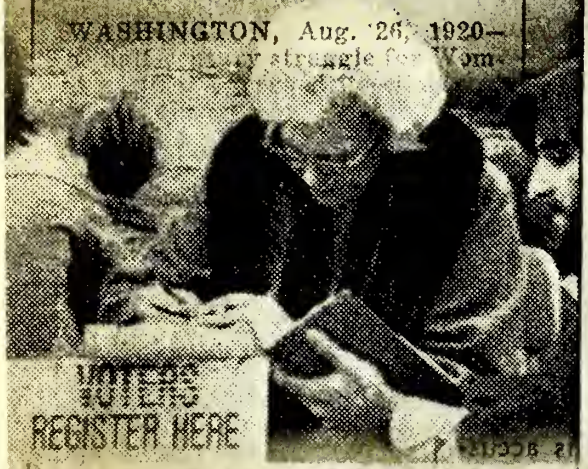

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The President, speaking in the auditorium of the War Memorial Opera House, built in memory of sons of the Golden Gate city who gave their lives in the first World War, in which he himself served, seemed to give unconscious expression to the solemn feeling of the occasion when, at the outset of his speech, he interpolated the words, half a hope, half a prayer:

"Oh, what a great day this can be in history!"

Just before the plenary session the President, accompanied, the

JOL SIGN the Dra Ends N

WASHINGTON, Jan. 27, 1973—"With the signing of the peace agreement in Paris today, and after receiving a report from the Secretary of the Army that

PATIENT PACKAGE INSERTS: A CONCEPT WHOSE TIME HAS COME?

The consumer's right to know is an irreversible and desirable trend of the Seventies. It extends, and properly, to a patient's right to know more about his or her prescription medications. One way, gaining favor, is through patient package inserts. Wisely-prepared and properly distributed when medically indicated, they could markedly improve patient knowledge and drug therapy—laudable goals by anyone's standards.

The PMA endorses these goals and will work with government, the health professions and consumers to achieve them.

The Advantages

The concept holds promise of benefits: better patient understanding of the product prescribed, better adherence to the treatment plan, and more awareness of possible side reactions.

Every doctor has had patients who fail to finish antibiotic regimens because they feel better. Some patients assume that if one tranquilizer or analgesic is good, two may be twice as good. Still others fail to report dizziness while on antihypertensive therapy —and so on.

Problems like these might arise less often if the patient received written information in addition to verbal instructions. Some studies suggest that patients are more receptive to such materials, and they more often understand the verbal instructions and follow them, when inserts are used.

The Disadvantages

There are also some potential problems. Obviously, the inserts must be clearly phrased, without extraneous or complex detail. How much information is enough? How can it be kept current? Should all patients receive the same information? Should inserts be included with all drugs? Should only potential problems be listed or are patients better off with a "fair balance" presentation that describes usefulness as well as drawbacks?

These and similar questions require answers, since model inserts have yet to be properly developed and tested. Despite the need for these studies, the FDA is proceeding prematurely with inserts on selected products. We think the Congress is the only place where the matter can be given the proper legal status and direction, particularly since it represents a conceptual change in the legal, medical and social framework of the nation's prescription drug information system.

The Solution

The PMA believes that carefully-devised pilot studies of various kinds of inserts are needed. They should be developed and implemented with full participation by doctors, pharmacists, consumers, communications experts and the drug industry. Such studies will provide reliable pathways to follow, so that inserts will be useful aids to medical practice.

And particularly we think that you should be closely involved in this debate and in these studies and decisions. Otherwise, people with less experience and qualifications may control the purposes, content and use of a tool with considerable promise for improved patient care. It could make a difference in your practice tomorrow, and more importantly, in the health of your patients.

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Tablets contain 5 mg (equivalent to 4 1 mg of fre base) or 2 5 mg (equivalent to 2.05 mg of free base) Brethine, brand of terbutaline sulfate

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Contraindications: Known hypersensitivity to sy pathomimetic amines.

Warnings: *Usage in Pregnancy:* The safety of th e of Brethine, brand of terbutaline sulfate, in human pre nancy has not been established. The use of the drug pregnancy, lactation, or women of childbearing potent quires that the expected therapeutic benefit of the dru weighed against its possible hazards to the mother or

Usage in Pediatrics: Brethine, brand of terbutalin fate, tablets are not presently recommended for childr below the age of twelve years due to insufficient clinic data in this pediatric group.

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This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

* **Indications:** When the combination represents the dosage determined by titration: Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, the nephrotic syndrome. Corticosteroid and estrogen-induced edema, idiopathic edema; hypertension, when the potassium sparing action of triamterene is warranted. (See Box Warning.) Routine use of diuretics in healthy pregnant women is inappropriate; they are indicated in pregnancy only when edema is due to pathological causes.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: **Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.** If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

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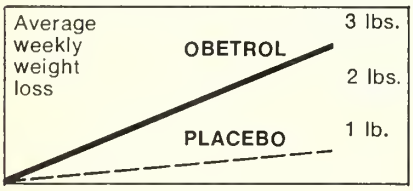

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Actions: Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. The anorectic effect diminishes after a few weeks.

Indications: Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.

Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.

Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic.* Urticaria. *Endocrine:* Impotence, changes in libido.

Dosage and Administration: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.

1. Narcolepsy: Usual dose 5 to 60 milligrams per day in divided doses.
2. Minimal brain dysfunction:
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   b. Children from 3 to 5 years of age: 2.5 milligrams daily raised in increments of 2.5 milligrams at weekly intervals until optimal response is obtained.
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3. Obesity: Usual adult dose 5 to 30 milligrams per day in divided doses.

Overdosage: Manifestations of acute overdosage with amphetamines include restlessness, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.

Management of acute amphetamine intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard.

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January 197

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ACNE CAN BE CURED—Gustave H. Hoehn, MD, Associate Clinical Professor of Dermatology, Loma Linda University School of Medicine. Arco Publishing Company, Inc., 219 Park Avenue South, New York City (10003), 1977. 144 pages, $7.95, Hardcover; $3.50 (Paperback).

ARGON LASER PHOTOCOAGULATION—H. Christian Zweng, MD, Palo Alto Retinal Medical Group, Inc.; Clinical Professor of Surgery (Ophthalmology), Stanford University School of Medicine; Hunter L. Little, MD, Palo Alto Retinal Medical Group, Inc.; Associate Clinical Professor of Surgery (Ophthalmology), Stanford University School of Medicine; in collaboration with Arthur Vassiliadis, PhD, Staff Scientist, Palo Alto Retinal Research Foundation, Menlo Park, California. The C. V. Mosby Company, Publishers, 3301 Washington Blvd., St. Louis (63103), 1977. 319 pages, $42.50.

BLOOD TRANSFUSIONS FOR CLINICIANS—John Wallace, BSc, MD (Edin), FRCP (Glas), FRCPath, Regional Director, Glasgow and West of Scotland Blood Transfusion Service; Honorary Lecturer, University of Glasgow; Honorary Consultant in Clinical Pathology, Greater Glasgow Health Board; Honorary Consultant to the Army; Examiner to The Royal College of Pathologists. Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th Street, New York, NY (10036), 1977. 351 pages, $22.50.

CLINICAL RADIOBIOLOGY—W. Duncan, FRCPE, FRCR, Professor of Radiotherapy, University of Edinburgh; Honorary Consultant Radiotherapist, Royal Infirmary and Western General Hospital, Edinburgh; and A. H. W. Kras, MA, DM(Oxford), DMRT, Consultant Medical Radiation Biologist, Glasgow Institute of Radiotherapeutics and Oncology, Belvidere Hospital, Glasgow; Honorary Clinical Lecturer, University of Glasgow. Churchill Livingstone-Medical Division, Longman Inc., 19 West 44th St., New York City (10036), 1977. 226 pages, $22.50.

COSTS, RISKS, AND BENEFITS OF SURGERY—Edited by John P. Bunker, MD, Professor of Anesthesia and Family, Community and Preventive Medicine, Stanford University School of Medicine; Benjamin A. Barnes, MD, Professor of Surgery, Tufts University School of Medicine; and Frederick Mosteller, PhD, Professor of Mathematical Statistics, Harvard University. Oxford University Press, 200 Madison Ave., New York City (10016), 1977. 401 pages, $8.95.

CURRENT CONCEPTS IN RADIOLOGY—Volume Three—Edited by E. James Potchen, MD, Chairman, Department of Radiology, Michigan State University, East Lansing. The C. V. Mosby Company, 3301 Washington Blvd., St. Louis (63103), 1977. 453 pages, $39.50.

CURRENT DIAGNOSIS—5—Edited by Howard F. Conn, MD, and Rex B. Conn, MD. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1977. 1272 pages, with 104 illustrations, $34.00.

CURRENT NEPHROLOGY—Volume 1—Edited by Harvey C. Gonick, MD, Adjunct Professor and Coordinator of Postgraduate Education in Nephrology, University of California, Los Angeles, Medical Center, Los Angeles. Pinecliff Publishing Co., 15415 Sunset Blvd., Pacific Palisades, CA (90272), 1977. 376 pages, $28.00.

CURRENT SURGICAL DIAGNOSIS AND TREATMENT—Third Edition—J. Englebert Dunphy, MD, Professor of Surgery Emeritus, University of California, San Francisco; Lawrence W. Way, MD, Professor of Surgery, University of California, San Francisco; and Associate Authors. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1977. 1140 pages, $[illegible].00.

GENERAL OPHTHALMOLOGY—8th Edition—Daniel Vaughan, MD, Clinical Professor of Ophthalmology, University of California School of Medicine, San Francisco; and Taylor Asbury, MD, Professor of Ophthalmology, Director, Department of Ophthalmology, College of Medicine, University of Cincinnati; illustrated by Laurel V. Schaubert. Lange Medical Publishers, Drawer L, Los Altos, CA (94022), 1977. 379 pages, $12.00.

THE HAND: Diagnosis and Indications—Graham Lister, FRCS, Assistant Clinical Professor of Plastic Surgery, University of Louisville; Consultant Hand Surgeon, University of Louisville Affiliated Hospitals. Churchill Livingstone-Medical Division, Longman Inc., 19 West 44th Street, New York City (10036), 1977. 224 pages, $27.50.

HANDBOOK OF MEDICAL TREATMENT—Fifteenth Edition—Edited by Simon J. Chatton, MD, Clinical Professor of Medicine, Stanford University School of Medicine. Jones Medical Publications, 355 Los Cerros Drive, Greenbrae, CA (94904), 1977. 634 pages, $9.00.

HANDBOOK OF OBSTETRICS AND GYNECOLOGY—Sixth Edition—Ralph C. Benson, MD, Clinical Professor of Obstetrics and Gynecology and Emeritus Chairman, Department of Obstetrics and Gynecology, University of Oregon Health Sciences Center, Portland. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1977. 772 pages, $9.50.

I ALMOST FEEL THIN—Albert J. Stunkard, MD, Professor, Institute of Neurological Sciences, University of Pennsylvania. Bull Publishing Co., P. O. Box 208, Palo Alto, CA (94302), 1977. 177 pages, $5.95 (softbound).

(Continued on Page 25)

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THE WESTERN
Journal of Medicine

Refer to: Calcaterra TC, Moseley JI, Rand RW: Cerebrospinal rhinorrhea—Extracranial surgical repair. West J Med 127: 279-283, Oct 1977

Cerebrospinal Rhinorrhea

Extracranial Surgical Repair

THOMAS C. CALCATERRA, MD; JOHN I. MOSELEY, MD, *and* ROBERT W. RAND, MD
Los Angeles

Cerebrospinal rhinorrhea is an uncommon complication of head trauma or of diverse types of intracranial diseases. Because of the risk of meningitis, this condition warrants immediate attention. If the leak fails to stop spontaneously in a short time, the precise site of the leak must be ascertained and surgical repair attempted. For the past 50 years craniotomy has been the principal operative approach; however, this method carries the risk of significant morbidity and protracted hospital stays, as well as a disappointing incidence of persistent leak. During the past decade extracranial operations for dural repair have been devised, and experience in the management of patients by a variety of such procedures illustrates the success of these operations.

A SPINAL FLUID LEAK from the intracranial space to the nasal respiratory tract is potentially very serious because of the risk of an ascending infection which could produce fulminant meningitis. The earliest attempts to seal these leaks were carried out extracranially by applying various cauterizing agents to the roof of the nose. Certainly most of these efforts were unsuccessful, although some authors reported cessation of rhinorrhea which may have been fortuitous or perhaps secondary to mucosal scarring.[1] After Dandy[2] documented the first successful intracranial repair of a cerebrospinal fluid (CSF) leak in 1926, management of this condition was almost exclusively by craniotomy. However, with the advent of the operating microscope and more refined methods of localizing the dural defect, extracranial methods of dural repair became increasingly attractive because of their inherent reduced morbidity. Our experience at the University of California, Los Angeles, Hospital with 14 patients in whom various extracranial operations were carried out during the past five years is presented.

From the Department of Surgery, Divisions of Head and Neck Surgery and Neurosurgery, University of California, Los Angeles, School of Medicine.

Submitted, revised, February 10, 1977.

Reprint requests to: Thomas C. Calcaterra, MD, Department of Surgery, University of California, Los Angeles, Center for the Health Sciences, Los Angeles, CA 90024.

Causes

Skull trauma with dural tearing is unequivocally the most common cause of cerebrospinal rhinorrhea. Usually the fracture involves some portion of the anterior cranial fossa floor with the leaks occurring through the cribriform plate or ethmoid sinus roof into the nose. Another frequently seen anterior fossa fracture site is the posterior wall of the frontal sinus through which CSF can escape into the nose via the nasofrontal duct. Less common are middle cranial fossa fractures that can cause leakage to the nose via the sphenoid sinus or eustachian tube. Such leakage may also occur when there is a fracture of the petrous bone allowing fluid to enter the mastoid

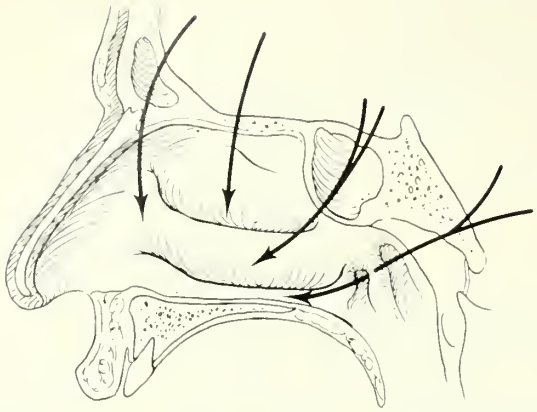

Figure 1.—Pathways of cerebrospinal fluid (CSF) leakage. Arrows show varied routes of CSF leaks to the nasal cavity.

air system. If the tympanic membrane is torn, the fluid will exit through the external ear canal; however, if the membrane is intact, spinal fluid will escape through the eustachian tube (Figure 1). For reasons that are not well understood, cerebrospinal rhinorrhea may occur as late as several months after skull fracture; this phenomenon was observed in three of our patients.

Included in the trauma category is iatrogenic cerebrospinal rhinorrhea, as seen in five of our patients (Table 1). This complication may follow extracranial surgical procedures such as sinus and mastoid operations. Likewise, intracranial operations may also involve dural tearing that permits leakage into the upper respiratory tract.

Nontraumatic cerebrospinal fluid fistulae tend to occur less frequently, and most of them are related to diseases that cause increased intracranial pressure or local skull destruction. Such conditions include hydrocephalus, primary or metastatic intracranial tumors, osteomyelitis of the skull and brain cysts. Congenital defects of the skull can also serve as the source of fistulae, usually occurring in the anterior cranial fossa. These are believed to represent mesodermal development disorders, inasmuch as dura and bone develop from this layer while pia and arachnoid develop from ectoderm.[3]

Diagnosis

Confirming the presence of cerebrospinal rhinorrhea is usually not difficult, particularly when there are antecedent factors such as head trauma or surgical operation, or when there is a clear watery discharge draining from one nostril. Often the spinal fluid can be initiated or increased by a Valsalva maneuver or by compression of both jugular veins. However, glucose determination made by glucose oxidase test papers is unreliable because of the reducing substances present in lacrimal gland secretions and nasal mucus. Quantitative glucose and protein determination of the suspected nasal fluid should therefore be done to confirm the diagnosis.

The precise localization of the dural defect is far more challenging. Factors in the patient's history may be helpful in identifying the site of the leak. A gush of fluid that occurs when the head changes position suggests a collection of fluid in one of the sinuses, particularly the sphenoid. A deficient sense of smell indicates an injury near the olfactory area, while a sense of fullness in the ear or a hearing loss implicates CSF in the middle ear.

Tomography of the paranasal sinuses or the base of the skull, or both, may show there to be an osseous defect or pneumocephalus. A sinus

TABLE 1.—*Extracranial Management of Cerebrospinal Fluid Leaks*

Patient and Site	*Cause*	*Operation*
1. postfrontal wall	blunt trauma	frontal osteoplastic flap and external ethoidectomy
2. postfrontal wall	blunt trauma	frontal osteoplastic flap
3. lateral recess frontal sinus	craniotomy	frontal osteoplastic flap
4. ethmoid roof	blunt trauma	external ethmoidectomy
5. ethmoid roof	blunt trauma	external ethmoidectomy
6. ethmoid roof	intranasal ethmoid surgical operation	external ethmoidectomy
7. cribriform plate	spontaneous	external ethmoidectomy plus tissue glue
8. cribriform plate	blunt trauma	external ethmoidectomy plus tissue glue
9. sphenoid sinus	blunt trauma	transseptal sphenoidotomy
10. spehnoid sinus	idiopathic	external ethmoidectomy and sphenoidotomy
11. petrous apex	craniotomy	tympanic cavity obliteration
12. petrous apex	craniotomy	tympanic cavity obliteration
13. petrous tegman	mastoid operation	mastoidectomy and temporalis muscle flap
14. petrous tegman	gunshot	mastoidectomy and temporalis muscle flap

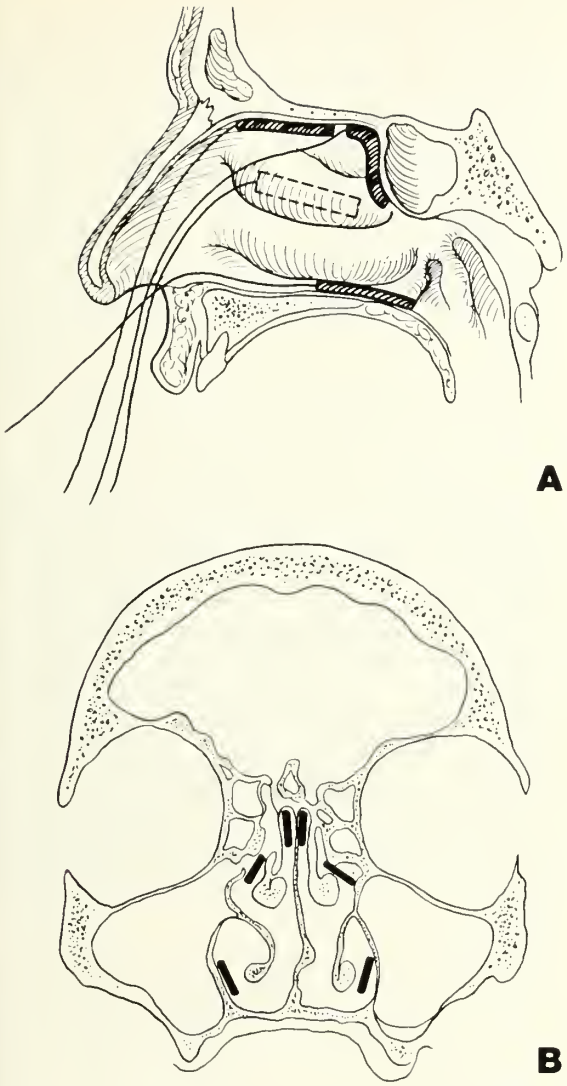

Figure 2.—Placement of cottonoid pledgets. **A,** Sagittal view of the nasal cavity showing anatomic location of pledgets. **B,** Coronal view of nasal cavity showing the same pledgets.

adjacent to a CSF leak can show increased density or an air-fluid level. The sugar content of the spinal fluid may cause local sinus mucosal edema which can be documented by radiographs.[4]

Injection of various types of marking substances into the intrathecal space has been utilized to localize the dural defect. Although radioisotopes are helpful in determining whether a leak is present, they often cannot show the fine detail required to localize the site of the leak. In our experience, vital dyes such as fluoresceine or indigo carmine used in conjunction with cottonoid pledgets which are placed strategically in the nose have provided the best information. In this procedure, the nasal cavities are sprayed with a 4-percent solution of cocaine to anesthetize and shrink the mucous membranes. Cottonoid pledgets are then placed into the (1) anterior roof of the nose, (2) posterior roof and sphenoethmoid recess and (3) middle meatus (Figure 2).

A lumbar puncture is then done and the opening pressure recorded (it may be quite low if the leak is copious). At least 10 ml of spinal fluid is withdrawn, mixed with dye, and then slowly reinjected into the intrathecal space. After the patient has been recumbent for about 30 minutes, his nose is examined and the cottonoid pledgets are removed. The area of cottonoid staining identifies the site of the leak. Staining of the pledget in the middle meatus indicates a leak of the frontal sinus. If the anterior nasal roof cottonoid is stained, a leak exists at the cribriform plate or anterior ethmoid roof. When the pledgets placed in the posterior nasal roof and sphenoethmoid recess are discolored, the posterior ethmoid region or sphenoid sinus is involved. Staining of the posterior pharyngeal wall suggests that fluid is emanating via the eustachian tube. Dye may also be seen behind the tympanic membrane.

Patients and Methods

Since 1970 the authors have carried out extracranial operations at UCLA Hospital on 14 patients to repair persistent CSF leakage. Other patients with this condition were seen during this period; however, in those cases the leak was stopped either by conservative management or by craniotomy (generally done in the earlier years of the series). The location of the leak and the methods of surgical repair are summarized in Table 1.

Treatment

Acute leaks resulting from head trauma or various types of cranial surgical procedures were managed conservatively whenever possible. This treatment generally consisted of a two-week trial of bedrest in a semisitting position, lumbar taps twice a day or continuous spinal fluid drainage, and administration of prophylactic antibiotics. These patients were cautioned against nose-blowing, sneezing and straining. On the other hand, immediate repair of the dura was done in those patients who had suffered severe cranial injury necessitating operative intervention for other reasons, if the leak was associated with intracranial air or complicated by meningitis. In the latter instance, the operative procedure was car-

ried out as soon as the meningitis had been completely cleared by antibiotic therapy.

A trial of conservative management was not necessarily considered for patients in whom the leak followed a head injury by several days or there was no history of head trauma, inasmuch as these conditions rarely heal spontaneously. Those patients with nontraumatic leaks in whom the source of the leak was not apparent were admitted to the neurosurgical service for complete evaluation to determine if an occult intracranial lesion was present.

As we gained experience with the management of CFS leakage, we employed extracranial methods of repair more often because of their reduced morbidity. As in the case of an intracranial repair, it is extremely important to precisely locate the dural defect before the operation, to assure selection of an appropriate extracranial approach which would afford maximum exposure of the dural dehiscence. Likewise, in order to pinpoint the dural defect intraoperatively, intrathecal dye was injected during the operation; this was done just after induction of general anesthesia. An indwelling catheter was placed in the lumbar subarachnoid space, and about 30 minutes before the anticipated exposure of the dural leakage site, spinal-fluid-diluted dye was slowly injected. By the time the leak was exposed, a discrete flow of dye-stained spinal fluid was seen trickling from the dural defect. The anesthesiologist can augment this flow by applying prolonged positive pressure ventilation to the patient. Without staining the spinal fluid, small leaks may not be visible, particularly if absolute hemostasis cannot be achieved in the operative field. The indwelling spinal catheter serves a second purpose by permitting continuous drainage for three to five days after operation, thereby maintaining a low spinal fluid pressure and insuring better healing of the dural repair.

Operative Experience

The extracranial surgical procedures in this series were done to repair leakage from four anatomic sites: (1) frontal sinus, (2) cribriform plate and ethmoid roof, (3) sphenoid sinus and (4) petrous bone.

Frontal Sinus

In three patients there was leakage through the frontal sinus. In all of them it was secondary to traumatic tears of the dura over the frontal lobe. An extracranial approach to this area was accomplished with an osteoplastic frontal bone flap through a coronal scalp or eyebrow incision.[5] This operation enabled visualization of the posterior wall of the frontal sinus where the bony defect was found. The area of the dural tear was exposed by removing adjacent bone with a drill burr or forceps; closure of dura was accomplished by direct suture approximation or by mattress suture of a connective tissue graft such as a frontalis fascia. To further ensure the seal, the frontal sinus may be packed with fat after all mucous membrane has been removed.

Cribriform Plate and Ethmoid Roof

Five patients were found to have leaks from this region and in all exploration was carried out through a curved naso-orbital incision. Access to the ethmoid roof or the cribriform plate required a complete ethmoidectomy. Leaks at either site were sealed with mucoperiosteal flaps rotated either from the lateral nasal wall or the nasal septum. The operating microscope greatly facilitated visualization of the leak as well as manipulation of the flaps (which on two occasions were secured with tissue adhesives). Further stabilization of the flaps was obtained with absorbable packing such as oxidized cellulose (Surgicel®).

Sphenoid Sinus

Two patients in the series had CSF leaks through the sphenoid sinus. In one patient the defect was approached between the septal membranes[6] and in the other through the ethmoid sinuses.[7] The transseptal approach has the advantage of avoiding a facial incision and allows sphenoid sinus packing without an open communication with the nasal cavity. However, if the leak cannot be precisely localized to the sphenoid sinus by preoperative studies, then it is better to approach this region through the ethmoid sinuses. In either case, the intersinus septum is removed and the sphenoid sinus denuded of its mucosa under visualization with the operating microscope. The sinus is then packed with thigh muscle fragments buttressed by septal bone.

Petrous Bone

Almost all of the dura surrounding the petrous bone can be approached extracranially from below. In four patients in this series there were leaks from dural defects adjacent to the petrous bone, two of which were repaired by direct dural

exposure by mastoidectomy. In two others packing of the eustachian tube through the middle ear was done to seal the leak.[8] With mastoidectomy, the dural defect is covered with fascia buttressed by a temporalis muscle pedicle. Sealing the eustachian tube and middle ear through the auditory canal will effectively prevent CSF from entering the pharynx; however, this technique should be used only in patients who have a permanent total hearing loss.

Results

An extracranial operation successfully achieved permanent sealing of the spinal fluid leak in all 14 patients. There were no significant postoperative complications. Although in patient 1 (Table 1) a successful repair of a leak through a frontal sinus fracture was achieved, another unexpected leak through the ethmoid roof had to be closed after the initial operation. The first attempt to seal the defect in patient 2 (Table 1) failed, but a second operation using the same approach was successful. Intracranial repair of the dural defect by craniotomy had been attempted previously in six of the patients. The follow-up periods ranged from four months to seven years, and there have been no instances of leak recurrence.

Summary

Successful management of cerebrospinal fluid rhinorrhea begins with a thorough diagnostic evaluation to determine the cause of the leak when it is not evident and to locate precisely the site of the leak if spontaneous cessation does not occur. Topographic mapping of the nasal fossa with strategically placed cottonoid pledgets to detect the leakage site of stained spinal fluid has proved invaluable in locating the dural defect. If the leak is not secondary to a brain tumor, our experience strongly suggests that the initial method of repair should be an extracranial operation selected to provide maximum exposure of the dural defect. This therapy will result in shorter hospital stays, less patient morbidity and a higher percentage of initial successful repairs.

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Cardiac Myxomas

Report of Eight Cases with Successful Excision

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Early diagnosis of atrial myxoma can be made by a high index of suspicion in patients in whom embolic phenomena, systemic manifestations, syncope, or suspected mitral or tricuspid valvular disease are noted. When the presence of an atrial myxoma is suspected, echocardiographic evaluation should be done promptly. This noninvasive technique has no morbidity or mortality and is accurate in greater than 90 percent of cases.

SINCE JANUARY 1964 excision has been carried out successfully in eight patients with cardiac myxoma at Loma Linda University Medical Center (LLUMC). Correct preoperative diagnosis was achieved in all, and there have been no recurrences. These cases are used as a basis for analyzing the modes of presentation and the course of right sided and left sided atrial myxomas.

Cardiac myxoma occurs with an incidence of 1/10,000 autopsies and the surgical survival in cases with correct preoperative diagnosis is substantially better (91 percent) than those in which the diagnosis was made at operation for suspected mitral valve disease (81 percent), as shown by a recent review of the past decade of surgical treatment of myxoma.[1]

Reports of Cases

Left Atrial Myxomas

CASE 1. A 9-year-old Puerto Rican girl was admitted to Loma Linda University Medical Center (LLUMC) on November 29, 1966, from a hospital in Puerto Rico.

Her first admission to hospital (in Puerto Rico) was in May 1966 for "probable rheumatic fever" with joint pains, nose bleeds, fever, fatigue and anorexia. The antistreptolysin O (ASO) titer was 1:625 and the erythrocyte sedimentation rate was 46 mm per minute. There was good response to treatment with penicillin, aspirin and steroids. In September 1966 she was readmitted because of an embolus to the left arm, which was removed surgically with good results. Her third admission to a Puerto Rican hospital was for the sudden onset of a severe headache, followed by pronounced lethargy, with receptive and expressive aphasia. After clinical resolution an angiocardiogram was done which suggested an intracavitary abnormality of the heart.

Physical examination on transfer to LLUMC on November 29, 1966, showed normal first and second heart sounds, a faint early diastolic sound, and a short midsystolic murmur at the lower left sternal border; one examiner heard a grade II/IV diastolic murmur at the apex. Small erythematous macules were noted on her left hand, with some cyanotic areas. Cineangiogram with pulmonary artery injection showed the presence of left atrial mass.

On December 1 the patient was taken to the

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operating room, where on cardiopulmonary bypass a friable gelatinous 3 by 4 cm tumor was removed. A broad pedicle was dissected away from the atrial septum where it was attached to the fossa ovalis. She was discharged in good condition eight days postoperatively.

CASE 2. A 31-year-old woman was admitted on June 20, 1968. She had had recurrent pulmonary infections over the past five years, and during the last 15 months had had progressive dyspnea on exertion, two pillow orthopnea, nocturnal dyspnea, pedal edema, fatiguability and a constant substernal pain. On physical examination a moderate right ventricular lift, a slight left ventricular lift and a palpable pulsation of the pulmonary artery were noted. The first sound and the pulmonary component of the second sound were both increased. There was a prominent early diastolic sound. A grade II/VI pansystolic murmur and a grade I/VI diastolic rumble were heard at the apex. On cardiac catheterization the pulmonary artery pressure was 34/14 mm of mercury and a pulmonary artery contrast media injection documented a filling defect in the left atrium on the angiogram. On June 28 the patient was taken to surgery, where, using cardiopulmonary bypass, a 5 cm globular myxoma, greenish tan in appearance, was removed. It was attached to the septum by a wide stalk, which was removed with a layer of atrial septal endocardium. She was discharged in good condition on the 12th postoperative day.

CASE 3. A 46-year-old woman was admitted on March 5, 1969, as a transfer from another hospital. (This case has been reported previously by Drs. Thompson and Simmons.[2])

During the first week of February 1969 the patient had had sudden onset of pain in the right eye, right side of the head and the left arm. On physical examination slurred speech and a cool pulseless left hand were noted. Results of cardiac examination were described on one occasion to be entirely normal except for a high pitched early diastolic sound. On another occasion a soft systolic murmur was heard at the left sternal border, which was not transmitted. Histologic examination of emboli removed from the right internal carotid and the left proximal brachial arteries showed tissue consistent with a cardiac myxoma. Cardiac catheterization and angiocardiography showed no abnormalities.

On March 17, 1969, the patient was taken to the operating room and cardiopulmonary bypass was established. At the junction of the posterior mitral valve leaflet and the posterior atrial wall there was an area about 14 mm in circumference, roughly round, where there appeared to have been friable tissue which had broken away. There remained a few friable projections, measuring up to 3 to 4 mm, and these were removed. Recovery was uneventful and she was discharged on the 13th postoperative day.

A repeat angiocardiogram was done in May 1974 because of bruits found on routine periodic physical examination by her private physician. Occlusion of the right internal carotid with cross filling from the anterior and middle cerebral systems was shown. The left axillary had occluded with distal reconstitution of brachial arteries to collaterals, with a possible false aneurysm forming just distal to the site of occlusion. She had no symptoms and no therapy was given.

CASE 4. A 54-year-old man was admitted on April 12, 1971, for exertional dyspnea, which had been present for a year and a half, paroxysmal nocturnal dyspnea six to eight months and occasional vague chest pain. On physical examination increased intensity of the first heart sound, a normal second heart sound and a faint intermittent early diastolic sound were noted. There was a grade II/VI middiastolic rumble with presystolic accentuation at the apex. A cardiovascular stress test (bicycle ergometer) on March 18 showed him to have normal exercise tolerance. He was able to exercise at 175 watts, and no signs of myocardial ischemia were seen on an electrocardiogram. Cardiac catheterization showed a systolic pulmonary artery pressure of 61 mm of mercury, and a large left atrial filling defect was shown on an angiocardiogram following pulmonary artery contrast media injection.

On April 22 the patient was taken to the operating room where, under cardiopulmonary bypass, a soft gelatinous gray-brown myxoma measuring 8 by 5 by 4 cm was removed. This was attached to the atrial septum in two places. The larger attachment was 2 cm above the mitral valve, and the secondary attachment was 1 cm higher on the septum. The pedicles and a layer of endocardium were removed, without creating a defect in the atrial septum. The postoperative course was uneventful and the patient was discharged on the eighth postoperative day.

CASE 5. A 67-year-old man was admitted on January 21, 1974, for evaluation of a calcified mass which appeared to be in the left atrium on

Figure 1.—Posteroanterior and lateral x-ray studies of the chest in case 5. Calcification is present in the region of the left atrium.

x-ray studies of the chest (see Figure 1) and follow-up tomography. He had been having episodes of dizziness associated with nausea, lasting about 20 minutes, and occurring two or three times a year for the ten years before admission. Symptoms had progressed during the five years before admission and included episodes of complete loss of consciousness and several grand mal seizures. On physical examination a totally irregular pulse with a rate of 120 per minute and a jugular venous pulse 4 cm above the sternal angle at 20 degrees were noted. A slight left ventricular heave was present. The first heart sound was split, and the second heart sound was normal. There were no murmurs. Cardiac catheterization with angiocardiography demonstrated a large left atrial filling defect. Echocardiography (see Figure 2) confirmed the presence of an atrial mass.

On February 22 the patient was taken to the operating room where on cardiopulmonary bypass a 5 by 5.4 by 4.5 cm grayish pink, nonfriable myxoma was removed (see Figure 3). Thrombus was present between the myxoma and the lateral part of the left atrial wall which partially enveloped a 3 by 4 cm area of the myxoma. The pedicle had a single attachment to the posterior atrial wall below the right inferior pulmonary vein. This was removed with a layer of endocardium. The postoperative course was uneventful although immediately after operation the patient had periods of confusion and disorientation. He was discharged on the 13th postoperative day. Atrial flutter was converted electrically to sinus rhythm several months after therapy with quinidine had failed to maintain sinus rhythm. Quinidine administration was discontinued because of thrombocytopenia. The patient was treated with prednisone for a short period with a good platelet response.

Case 6. A 63-year-old woman was transferred from another hospital on March 5, 1974 because of multiple arterial emboli. She had had rheumatic fever at age five. A diagnosis of rheumatic heart disease with mild mitral insufficiency and possible minimal aortic stenosis had been made when the patient was seen as an outpatient five years before admission. Thirteen days before admission an acute inferior myocardial infarction had occurred. Embolism to the left subclavian artery occurred one day after the infarct, and to the right posterior tibial artery one day later. These were excised, but there was a poor response to the second embolectomy. The patient was transferred to Loma Linda University Medical Center where angiography showed an aortic saddle embolus and a right popliteal embolus. The day after admission the aortic saddle embolus was removed under general anesthesia. Findings on histologic examination of the embolus were consistent with car-

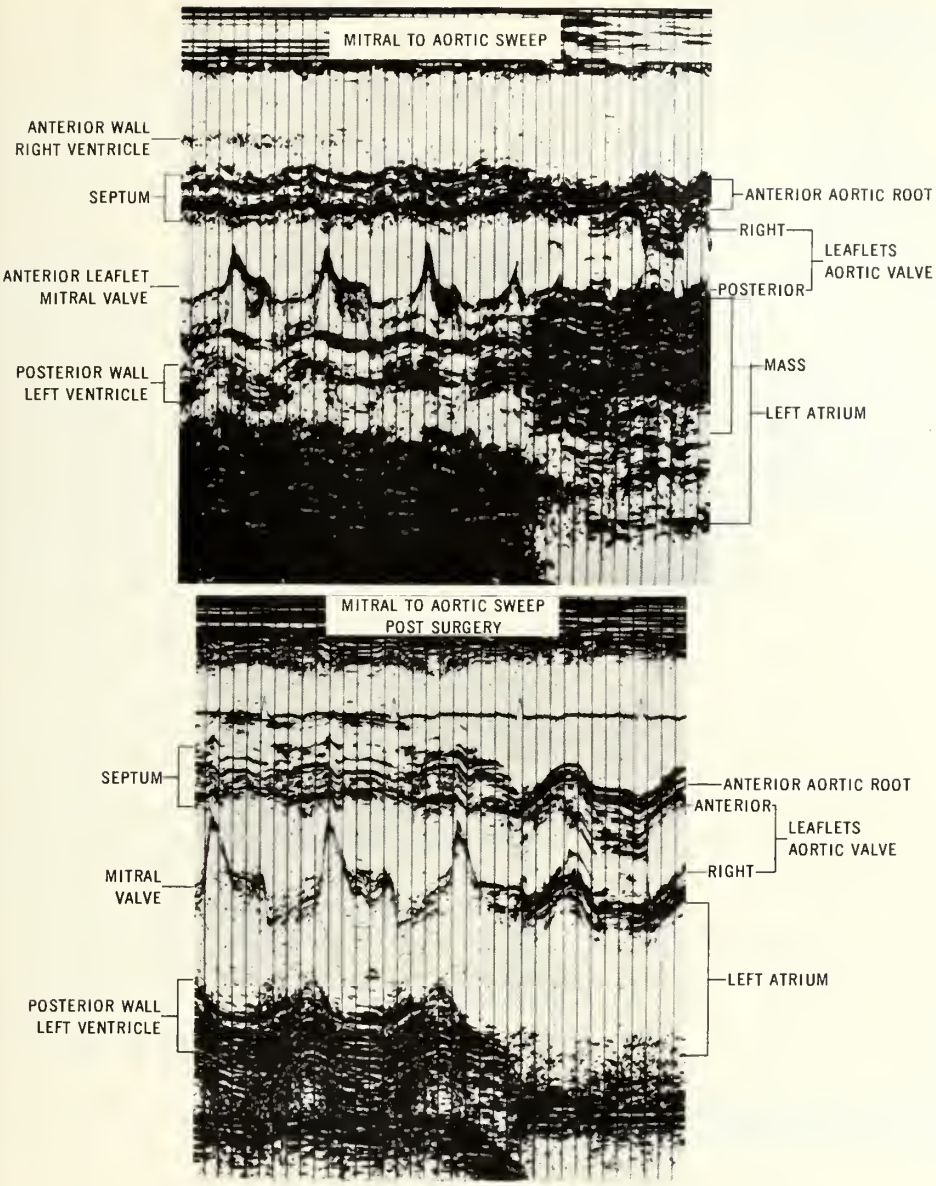

Figure 2. — Preoperative and postoperative echocardiograms, case 5. Dense mass in the left atrium before operation is absent in the postoperative sweep.

diac myxoma, and a left atrial myxoma was shown with angiocardiography. This myxoma could not be identified on an echocardiogram. The right leg became gangrenous and amputation below the knee was required.

On March 27 the patient was taken to the operating room, where on cardiopulmonary bypass a friable myxoma, 1.5 cm in diameter, which did not prolapse through the mitral valve was removed. A segment of the atrial septum at the base of the pedicle was removed, and the defect closed with sutures. There was no evidence of rheumatic valvular disease at operation. The postoperative course was complicated by a pleural effusion which was treated by thoracentesis, and the patient was discharged on the 21st postoperative day.

Right Atrial Myxoma

Case 7. A 60-year-old man was admitted on August 17, 1970, for further evaluation of progressive dyspnea. Syncopal episodes had first occurred in December 1967. Right and left heart catheterization in June 1968 was not diagnostic. Because of increasing memory loss, weakness, weight loss, orthopnea and dyspnea, which was noted both on changing positon and on exertion after walking one block, reevaluation was done. On physical examination the patient was cachectic with an elevated jugular venous pulse with

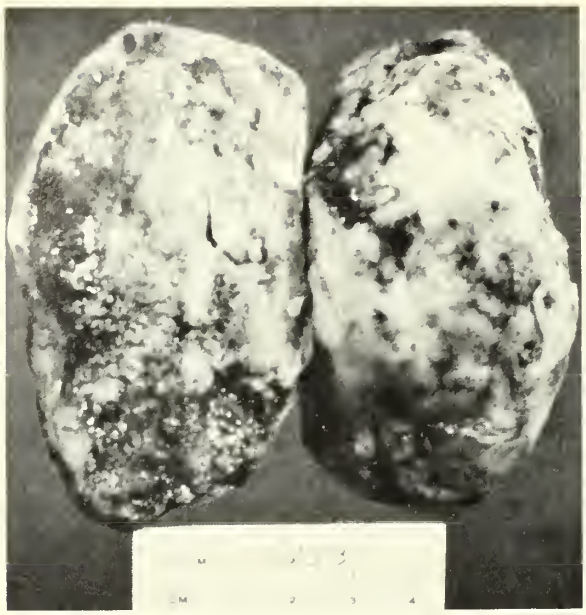

Figure 3.—Gross specimen of myxoma, bisected, from case 5.

prominent V waves, 8 cm above the sternal angle at 30 degrees. Cardiac examination showed a left parasternal heave and at the lower left sternal border a third heart sound, a grade I/VI systolic murmur and a grade II/VI diastolic murmur. The liver was palpable 6 cm below the right costal margin.

Cardiac catheterization with right atrial angiography showed a calcified right atrial mass, and tricuspid regurgitation. Cardiac output was 1.66 liters per minute. An echocardiogram confirmed the presence of a right atrial mass. On August 31, 1970, the patient was taken to the operating room where an 8 by 6 by 5 cm myxoma, filling most of the right atrium, was excised under cardiopulmonary bypass. A small portion of the atrial septum, near the fossa ovalis, was excised with the tumor pedicle and the defect sutured closed (See Table 1).

Case 8. A 57-year-old woman was admitted to hospital on June 19, 1976, because of syncopal episodes. For several years she had been crippled by a spinal cord disease involving the posterior and lateral columns, but results on a Schilling test were normal. For one month before admission there had been syncopal episodes. These occurred chiefly when the patient was standing but later occurred when she was sitting or recumbent. In the two weeks before entry two episodes of syncope had occurred. Following her admission to hospital a syncopal episode occurred with pronounced hypotension. Systolic blood pressure dropped to 40 mm of mercury.

On examination the right ventricle was palpable in the epigastrium. The first heart sound was loud and there was a fourth heart sound. There was a low frequency harsh midsystolic ejection murmur in the right parasternal area. A sedimentation rate showed borderline elevation. Serum protein electrophoresis showed a total protein value of 5.5 grams per 100 ml, an albumin of 2.9 grams per 100 ml and a gammaglobulin of 1.1 grams per 100 ml. An electrocardiogram showed right atrial enlargement, a tendency to right axis

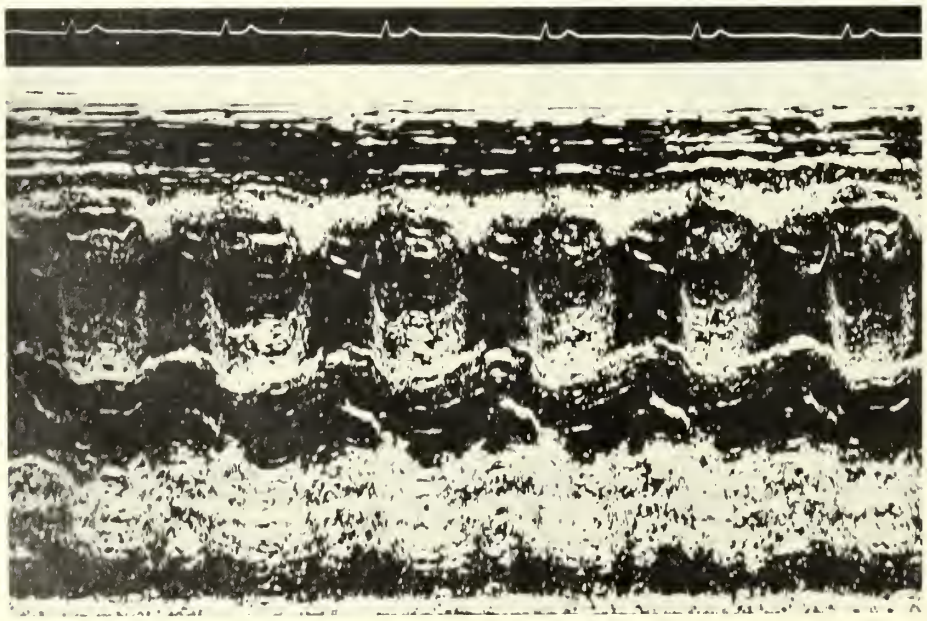

Figure 4. — Echocardiogram showing myxoma of right atrium.

TABLE 1.—*Summary of Clinical and Laboratory Features*

Left atrial myxomas—Cases #1-6

Pt. No./Age/Sex	Obstructive Symptoms	Emboli Location	Systemic Manifestations	Physical Findings	Laboratory: Anemia	Laboratory: ESR	Laboratory: Serum Proteins Abnormal	Laboratory: Echo Cardiography	Laboratory: Ca^{+2} by X-Ray	Laboratory: EKG	Catheter Data mmHg: PA	Catheter Data mmHg: Wedge
1. 9 ♀	None	#1 Left brachial, #2 Cerebral	Fever, arthralgia, fatigue, anorexia	Faint EDS, short midsystolic M at LSB	−	+	+	ND	−	RVH	ND	ND
2. 31 ♀	DOE, orthopnea, PND, recurrent pneumonia	None	Weight loss, fever, chest pain, fatiguability	RV and LV heaves ↑S1, ↑P2 at apex	−	−	+	ND	−	Early RVH	85/50	20
3.* 46 ♀	None	Right internal carotid Left brachial	None	EDS, variable systolic M. at LSB	0	+	−	ND	−	Normal	25/5	10
4. 54 ♂	DOE PND	None	None	↑S1, EDS, DM at apex	+	+	+	ND	−	RVH LAH	61/23	31
5. 67 ♂	None	Episodic small cerebral emboli	None	Normal findings on cardiac examination	+	+	ND	+	+	Atrial fib.	35/18	18
6. 63 ♀	None	Coronary, left forearm, aortic bifurcation, right popliteal	None	↑S2, Grade II, SM apex→axilla	+	+	ND	−	−	Acute diaphragmatic infarct, antero-lateral ischemia	31/10	7
7. 60 ♂	DOE, orthopnea, PND, syncope	None	Weight loss, weakness	Prominent jugular V wave EDS, left parasternal heave, grade II DM	+	+	+	+	+	Atrial Fib. RBBB	"Normal"	"Normal"
8. 57 ♀	Syncope with ↓BP (systolic=40)	None	None	RV epigastric heave, ↑S1, harsh mid-systolic M Right para-sternal area	−	+	+	+	−	Right atrial enlarge-ment, possible RVH	"Low"	ND

Ca^{+2}=calcification; DM=diastolic murmur; DOE=dyspnea on exertion; EDS=early diastolic sound; ESR=erythrocyte sedimentation rate; Fib.=fibrillation; LAH=left atrial hypertrophy; LSB=left sternal border; LV=left ventricular; M=murmur; ND=not done; PA=pulmonary artery; PND=paroxysmal nocturnal dyspnea; ↑P2=increased intensity of pulmonic second sound; RBBB=right bundle branch block; RV=right ventricular; RVH=right ventricular hypertrophy; ↑S1=increased intensity of first heart sound; ↑S2=increased intensity of second heart sound; SM=systolic murmur; Wedge=mean PA wedge.

*Previously reported.[2]

deviation and possible right ventricular hypertrophy. An echocardiogram (Figure 4) done on June 25 showed an abnormal shadow. The report indicated that "the shadow could, indeed, be due to a mobile tumor in the right atrium lodging in the tricuspid valve during diastole." On right heart catheterization the pulmonary artery and right ventricular pressures were both low. The right atrial mean pressure was 10 mm of mercury. A single contrast injection at the orifice of the superior vena cava showed a large tumor mass within the right atrium which prolapsed through the tricuspid orifice during diastole and swung back towards the right atrium during ventricular systole.

On June 29 a 7.5 by 5.5 by 4.5 cm yellow tan friable mass attached to the fossa ovalis of the atrial septum was surgically removed under cardiopulmonary bypass. The myxoma was removed with a 1 cm margin and a 2 by 3 cm woven dacron patch was sutured into the surgical defect in the atrial septum. At the time of operation a pacemaker was implanted. The patient made an uncomplicated recovery from the surgical procedures but still remained crippled from neurological disease. She was discharged on July 14 (see Table 1).

Comment

Crafoord in 1954 was the first to successfully excise a cardiac myxoma.[3] Angiocardiography was first used in the diagnosis of myxoma in 1950,[4] and echocardiography in 1968.[5] As more cases are being reported, a better idea of the clinical features has become available.

Left Atrial Myxoma

The clinical features of cardiac myxomas are related to systemic manifestations, hemodynamic obstruction or embolic phenomena.

MacGregor first described the systemic manifestations of weight loss, fever, anemia, increased sedimentation rate and elevated globulins.[6] Our first case was in this category, but was exceptional in the degree to which it mimicked acute rheumatic fever. Joint pains, elevated ASO titer, and epistaxis in a 9-year-old patient must be caused very rarely by myxoma, because no similar cases were encountered in a recent comprehensive review of the literature of myxomas treated surgically.[1] Cobbs alludes to personal experience with a myxoma case in which the symptoms were those of rheumatic fever, but he does not give details.[7] A myxoma has been reported in conjunction with rheumatic heart disease, but there was no evidence of rheumatic involvement in our patient at operation. Prominent systemic manifestations were also present in Cases 2 and 4.

The hemodynamic manifestations mimic mitral or tricupsid valve disease, depending on the location of the myxoma. In cases 2 and 4 there were left atrial myxomas with mitral murmurs, and notably elevated pulmonary artery pressures (85 and 61 mm of mercury, respectively).

Embolic phenomena occurred in cases 1, 3, 5 and 6, or two thirds of the left atrial myxomas in our series. This is an incidence of embolization comparable to the 59 percent recently reported for left atrial myxomas.[1] Suspected coronary artery embolism with acute myocardial infarction, as occurred in case 6, is very unusual, and has only been reported twice in the operative myxoma literature of the past decade.[8,9] The diagnosis of atrial myxoma was made by histologic examination of embolic material in three of our cases (1, 3 and 6).

Extensive calcification of myxoma which allows the diagnosis to be made on chest film or fluoroscopy was present in our patient with right atrial myxoma (case 4) and in one of our patients with left atrial myxomas. Calcification is far more common in right atrial myxomas (28 percent) than in left (8 percent).[1]

False negative results of echocardiography in our case 6 can be attributed to the fact that a large portion of the myxoma had embolized to various arterial sites including the aortic bifurcation. The remaining portion of the myxoma was small and did not prolapse through the mitral valve. The echocardiographic technique used by Sun to visualize nonprolapsing tumors,[10] which is sometimes technically very difficult, was not employed. Echocardiography is generally an accurate test for myxoma, and was positive in 49 of the last 54 cases in which surgical operation was done.

The pedicle usually arises from the atrial septum, near the margin of the fossa ovalis. This is used as one of the criteria for distinguishing myxoma from thrombus,[11] and is the basis for some of the theories of pathogenesis of myxoma.[12] Case 5 is an exception to this rule; in that case the pedicle arose from the posterior atrial wall below the right inferior pulmonary vein. In case 4 there were two pedicles, both arising from the atrial septum.

With the advent of echocardiography, there is now available a noninvasive procedure for evaluation in patients with mitral valve disease, syncope or suspected embolic phenomena. In case 5 there were normal findings on physical examination of the heart in the presence of a 5 by 5 cm myxoma. Symptoms had been present for ten years. In case 2 symptoms had been present for five years and were attributed to mitral valve disease. The patient in case 4 went to cardiac catheterization two years before the diagnosis was made at a subsequent study. During the past decade, 23 percent of the patients operated on for cardiac myxomas went to surgery with a presumed or cardiac catheterization "confirmed" diagnosis of mitral valve disease.[1] Earlier diagnosis, based on a high index of suspicion, and the more widespread use of echocardiography in the future should reduce the morbidity and mortality in groups such as these.

Right Atrial Myxoma

Characteristic hemodynamically obstructive elements were present in both of our cases of right atrial myxoma. Isolated tricuspid stenosis was present clinically in one case and this is very suggestive of right atrial myxoma.

Both patients also had syncope, which is more common in myxomas than in rheumatic valvular lesions.

Calcification had developed in the myxoma (in case 7) to the point that it could be recognized at fluoroscopy and with plain films by the time of the first heart catheterization, two years before. Calcification is far more common in right atrial myxomas (28 percent) than in left (8 percent).[1]

Results on echocardiography were positive, but (in case 7) the studies were done after angiocardiography had shown the presence of the tumor. Echocardiography is reportedly less useful in evaluating right sided heart tumors.[1] The tricuspid landmarks are more difficult to visualize than mitral landmarks, and in patients with large right sided tumors the anatomy of the heart may be distorted and tumors can be missed, or only suggested by ultrasound techniques.

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Pulmonary Toxicity of Antineoplastic Agents

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Pulmonary parenchymal or pleural reactions to chemotherapeutic agents used in the management of patients with malignant diseases are being recognized with increasing frequency. Alkylating agents, asparaginase, bleomycin, methotrexate and procarbazine have all been implicated. Some of the reactions, such as the rare procarbazine pleuritis and pneumonitis, represent hypersensitivity phenomena. Others, such as alkylating agent pulmonary toxicity, appear to be direct toxic effects of the drugs. The severity of the toxicity is variable. The appearance of these pulmonary changes must be differentiated from tumor progression or a variety of possible infections. The awareness of possible pulmonary toxicity is of great importance since early discontinuation of the agent following the first hint of pulmonary toxicity may allow partial or complete reversal of the process. Continued therapy in the face of drug-related pulmonary toxicity may enhance the likelihood of irreversible pulmonary compromise with respiratory failure and death.

NEW PULMONARY INFILTRATES, pleural effusions or mediastinal masses appearing in patients with cancer are of obvious importance. Especially during aggressive antitumor chemotherapy, appropriate diagnostic studies must be done and indicated therapy instituted with all deliberate speed, since several potentially responsible pulmonary processes may be rapidly life threatening. Pulmonary infection in such immunosuppressed and often granulocytopenic patients is of primary concern. Other frequently considered possibilities include pulmonary hemorrhage associated with thrombocytopenia, and single or multiple pulmonary emboli. The appearance of recurrent or progressive malignant disease is always kept in mind. In addition to these diagnoses, another possibility not to be overlooked, even in the face of acute and severe respiratory compromise, is a pulmonary reaction to one of the therapeutic agents used in the management of these patients.

In an extensive review of drug induced pulmonary disease, Rosenow[1] compiled a long list of diagnostic and therapeutic agents capable of inducing various types of pulmonary reactions. The list is impressive in its length and diversity. Several of the agents fall directly into the armamentarium of the oncologist.

Pulmonary Reactions After Antitumor Chemotherapy

Drug-induced pulmonary reactions may be broadly divided into allergic or hypersensitivity reactions on one side and direct toxic reactions on the other (see Table 1). Allergic phenomena

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ABBREVIATIONS USED IN TEXT

ALGB = Acute Leukemia Group B
ALL = acute lymphocytic leukemia
MOPP = mechlorethamine, vincristine (Oncovin®), procarbazine and prednisone

are recognized as occurring in a small percentage of patients receiving any drug. They are not dose dependent and are not a response to any specific pharmacologic action of the offending agent. Such hypersensitivity phenomena require an induction period before an initial allergic response, but full-blown recall evolves rapidly on reexposure to small amounts of the offending agent. Reactions often include a constellation of findings such as skin rash, urticaria, bronchospasm and serum sickness. Toxic reactions—true side effects of therapy—are most often tied directly to some desired pharmacologic action of the drug. These are usually dose dependent and can be produced in a substantial percentage of patients if a sufficient amount of the agent is given. Reexposure to small quantities of the drug will not lead to the rapid reappearance of all the toxic symptoms.[2]

Hypersensitivity Reactions

True allergic reactions are seen with asparaginase and procarbazine. L-asparaginase is most frequently used in the treatment of acute lymphocytic leukemia. A review of the early National Cancer Institute experience with repetitive doses of Escherichia coli asparaginase showed a 33 percent (9/27) incidence of hives and dyspnea in children receiving the drug.[3] Treatment with antihistamines (intravenously given benadryl) and steroids usually controlled the symptoms. Further E. coli asparaginase was withheld. More recently, a switch to Erwinia asparaginase (Porton) following a reaction to the E. coli material has allowed continued asparaginase therapy without another immediate allergic reaction.

The experience with asparaginase at Memorial Hospital for Cancer and Allied Disease was reviewed in 1970.[4] Pretherapy testing with intradermal asparaginase produced an immediate wheal and flare reaction in only one case. All other reactions occurred after at least several days of daily intravenous administration. Shortness of breath occurred in 22 percent of patients. X-ray studies of the chest in these patients were not commented upon. Other manifestations of hypersensitivity included urticaria (65 percent), hypotension (18 percent) and facial edema (11 percent). In their experience, control of symptoms with antihistamines allowed continued administration of the drug.

TABLE 1.—*Chemotherapeutic Agents Causing Pulmonary Reactions*

Drugs	*Mechanism of Reaction*
L-Asparaginase	Hypersensitivity
Procarbazine	Hypersensitivity
? Azathioprine	Hypersensitivity
Methotrexate	Uncertain
Bleomycin	Direct Pulmonary Toxicity
Busulfan	Direct Pulmonary Toxicity
Chlorambucil	Direct Pulmonary Toxicity
Cyclophosphamide	Direct Pulmonary Toxicity
Melphalan	Direct Pulmonary Toxicity

Procarbazine, a monoamine oxidase inhibitor, is an important drug in therapy of Hodgkin disease. It is also used for treatment of small cell carcinomas of the lung, non-Hodgkin lymphoma and central nervous system malignancies. Allergic reactions occur with procarbazine therapy. A pleuropulmonary component to procarbazine allergy was first described by Jones and co-workers in 1972.[5] In Jones' patient, a man with Hodgkin disease receiving MOPP (a combination of mechlorethamine, vincristine [Oncovin®], procarbazine and prednisone) chemotherapy, cough, fever and shortness of breath developed, along with pulmonary infiltrates and a pleural effusion on reexposure to procarbazine during his second and third cycles of MOPP. A challenge dose of procarbazine administered under controlled conditions also evoked the entire complex of respiratory signs and symptoms, thereby confirming the suspected diagnosis of procarbazine hypersensitivity.

Another case of hypersensitivity pneumonitis during combination chemotherapy including procarbazine has been reported.[6] In this patient open lung biopsy was done which showed a proliferative alveolar reaction including interstitial leukocyte infiltration, occasional eosinophils and alveolar septal edema. No fibrosis was present and the findings were compatible with an acute allergic pneumonitis. The patient recovered fully when administration of the drugs was discontinued. In light of Jones' case report, procarbazine was quite possibly responsible for this allergic process.

Imuran® (azathioprine) has also been implicated in one case report as a cause of allergic

pneumonitis. The patient had received six weeks of orally given Imuran and bilateral basilar shadows developed on x-ray studies of the chest, in addition to clinical respiratory distress. A pronounced decrease in forced expiratory volume and forced vital capacity was shown on pulmonary function testing. This syndrome was felt to be an allergic alveolitis secondary to Imuran administration.[7] The Imuran administration was discontinued and steroids were given (prednisone, 30 mg per day). The patient improved rapidly. After three months, findings on repeat x-ray study of the chest and pulmonary function studies had returned to within normal limits. Though possible, the causal role of Imuran therapy in this situation remains speculative.

Reactions of Uncertain Mechanism

Not yet clearly defined mechanistically as hypersensitivity phenomena or toxic side effects are the pulmonary reactions associated with intermittent methotrexate administration. In 1969, Acute Leukemia Group B (ALGB) reported follow-up on 93 patients with acute lymphocytic leukemia (ALL) in whom remission induction with vincristine and prednisone had been carried out followed by maintenance therapy with biweekly administration of methotrexate (30 mg per M^2) given either orally or intramuscularly.[8] During the maintenance phase, pulmonary infiltrates that lasted up to several weeks developed in 38 of the 93 patients. Three pulmonary-related deaths occurred. One was documented as a pneumocystitis pneumonia, but the other two were undiagnosed. The startling frequency of pulmonary reactions was completely unexplained, but the authors speculated that the lung changes were most likely infectious, with the high attack rate caused by either decreased intrinsic lung clearing capacity or altered immune status induced by the methotrexate.

Within six months of the ALGB results, Clarysee and associates[9] reported on seven consecutive patients with ALL in remission given methotrexate biweekly as maintenance therapy. In each patient there developed a severe respiratory illness, characterized by fever, nonproductive cough, dyspnea and cyanosis, that appeared 12 to 100 days after initiation of biweekly administration of methotrexate. X-ray studies of the chest in each case showed bilateral interstitial pulmonary infiltrates, more pronounced in the lower lobes. No pleural effusions were noted. Moderate eosinophilia was present in five of the seven patients. In five of the seven, methotrexate therapy was continued during the respiratory illness; in the sixth it was delayed for one week; in the seventh it was discontinued. Regardless of the handling of the methotrexate therapy, the course appeared to be essentially the same. The acute illness lasted ten to 40 days, followed by a period of rapid improvement. Complete clearing of symptoms and x-ray findings occurred in all but one patient.

In Clarysee's series,[9] open lung biopsy was done in one patient. Findings included a mixed inflammatory reaction within alveolar spaces and interstitial tissue. Multinucleate giant cells and noncaseating granulomas were present. The overall appearance was similar to the histologic appearance of lung biopsy material seen in syndromes of farmer's lung or pigeon-breeder's disease. Subsequently other cases with similar histology have been reported.[10,11]

In 1972 Whitcomb and co-workers[12] reviewed the literature on methotrexate pneumonitis and were able to add an additional six patients[10,13-15] to those described by Clarysee. These new reports included patients with underlying diseases other than acute leukemia. In each case methotrexate was given either weekly or biweekly for 12 to 196 days before the appearance of the respiratory illness. In contrast to the original seven patients of Clarysee,[9] five of these new patients received steroids (30 to 120 mg of prednisone per day) for the pneumonitis. In the steroid-treated patients, defervescence seemed to be more prompt, ranging from four to eight days rather than ten to 40 days, despite apparently equivalent initial clinical and radiographic presentations. In one of the steroid-treated patients, findings that had completely cleared at treatment with 30 mg per day of prednisone reappeared when the dosage was dropped to 10 mg per day on the fourth day of steroid therapy.[14] In that patient, administration of all medication, including steroids, was discontinued when the symptoms and chest findings recurred, and the patient's condition slowly improved over the subsequent ten days.

Recently, Sostman and associates[16] updated the status of methotrexate pneumonitis with a report of 36 cases. The findings were the same as in the earlier reports of Clarysee[9] and Whitcomb[12] except that Sostman found two patients with associated pleural effusions and three with hilar adenopathy. Findings from biopsy studies done in

several patients were similar to those in Clarysee's series except that in one patient frank pulmonary fibrosis was found.

Most patients in whom methotrexate pneumonitis develops have been receiving orally given methotrexate, but this complication has also been reported for intramuscular and intravenous administration as well. In addition, Gutin and associates[17] reported the case of a patient who was receiving methotrexate intrathecally every other day for meningeal carcinomatosis of breast origin; fever, cough and pulmonary infiltrates developed after ten doses of intrathecally given methotrexate over about three and a half weeks. Peripheral count suppression without marrow involvement with tumor was seen. Measurable levels of methotrexate were found in specimens of serum one to two days after an intrathecal dose. Postmortem evaluation of the lungs showed a pattern of interstitial pneumonitis with multinucleate giant cells suggesting methotrexate lung disease.

The cause of methotrexate lung disease remains uncertain. The popular notions of direct pulmonary toxicity or hypersensitivity phenomena do not explain the common findings that continuation of methotrexate therapy during the acute illness fails to perpetuate or worsen the condition and that reexposure to methotrexate is rarely associated with reappearance of pneumonitis. Sostman[16] has suggested that the timing of drug administration appears to affect the frequency of pulmonary reactions with more frequent doses resulting in a higher rate of pulmonary toxicity.

Toxic Side Effects

As opposed to the allergic reactions discussed earlier, more characteristic toxic reactions underlie the pulmonary disease induced by busulfan, cyclophosphamide, bleomycin, chlorambucil and melphalan.

In 1961, Oliner and co-workers[18] reported two patients with chronic myelogenous leukemia treated for 9 and 13 months respectively with busulfan (Myleran®) given daily. Following this therapy, each presented with the subacute appearance of cough, fever, shortness of breath, weakness and weight loss. Physical examinations showed diffuse rales, and x-ray films of the chest showed bilateral diffuse infiltrate.[5] Lung biopsy studies showed focal chronic interstitial pneumonitis and interstitial fibrosis. An atypical proliferative appearance of the cells lining the terminal bronchioles and alveolar septae was noted. Steroids provided symptomatic benefit in both patients, but the changes shown on x-ray studies regressed only in the patient who had the nine months of therapy. Many months later, this patient again received busulfan each day. Cough, fever and respiratory distress did not reappear.

By 1966 ten cases of busulfan pulmonary toxicity—so-called "busulfan lung"—had been reported.[18-21] Several more have been reported since.[22-26] Seven of the first ten patients had been treated with orally given busulfan each day for 9 to 30 months before respiratory complaints developed. The other three had received the drug intermittently over the preceding five to eight years. In each case the patients presented with combination of fever, chills, cough, weakness, weight loss and shortness of breath. Pulmonary infiltrates were noted on x-ray studies, and restrictive defects could be shown on pulmonary function testing. This clinical constellation is sufficient to support a diagnosis of "busulfan lung." Recently, Byrnes and associates[27] have shown that the clinical impression of "busulfan lung" can be confirmed by obtaining diagnostic pulmonary tissue through a transbronchial biopsy.

The true incidence of "busulfan lung" is unknown. In a study of 40 consecutive patients, treated daily with busulfan for a median duration of 19 months, who were examined at postmortem, in only one case were there clear-cut changes of busulfan pulmonary toxicity. That patient had been severely symptomatic following 30 months of busulfan therapy.[24]

A few reports[28,29] of lung toxicity following prolonged cyclophosphamide (Cytoxan®) therapy have also appeared. One[28] involved a 23-year-old woman with Hodgkin disease who received 50 to 150 mg of cyclophosphamide orally each day for 27 months. The reports of cyclophosphamide lung disease are very reminiscent clinically, radiographically and histologically of "busulfan lung," and a similar mechanism has been proposed.

Yet another alkylating agent, chlorambucil (Leukeran®), has also been associated with fibrotic pulmonary disease. In a brief letter in the *New England Journal of Medicine,* Rubio[30] reported the cases of four patients receiving long-term therapy with chlorambucil, duration and total doses unspecified, who died with severe interstitial pulmonary fibrosis. In one of the cases the syndrome of respiratory insufficiency was

said to evolve rather acutely. The possible use of steroids in these patients was not discussed.

Of the remaining polyfunctional alkylating agents, nitrogen mustard has not been implicated in the production of pulmonary fibrosis. However, the possible association of melphalan (L-phenylalanine mustard) and pulmonary fibrosis was reported by Codling and Chakera in 1972.[31] Recently a probable case of pulmonary fibrosis associated with melphalan treatment of multiple myeloma has been reported.[32]

Bleomycin (Blenoxane®) has gained wide acceptance as an antitumor agent because of a significant antitumor effect combined with minimal myelosuppression. The drug is concentrated in skin and lung, and these two tissues have been the major sites of bleomycin toxicity. The true frequency of clinical bleomycin pulmonary toxcity and dose-schedule or time dependent aspects to toxicity remain uncertain. Japanese investigators reporting on 462 patients[33] treated with bleomycin noted a 4.2 percent incidence of pulmonary fibrosis and a 1.5 percent incidence of respiratory failure. A European cooperative study[34] reported a 3.3 percent incidence of pulmonary complications. Rudders[35] reviewed the cases of 39 patients with lymphoma treated with bleomycin. Of Rudders' patients, acute fatal respiratory failure developed in one after 210 mg of drug was given. In three others, pulmonary infiltrates appeared during bleomycin therapy and administration of the drug was discontinued. The overall incidence of pulmonary injury attributed to bleomycin was 10.4 percent.

Findings from an extensive review of the pulmonary toxicity of bleomycin by DeLena[36] and colleagues suggested a much higher rate of objective bleomycin lung toxicity. They reported a 38.9 percent incidence of this complication, defined as either the appearance of rales, ronchi or pleural rubs in patients receiving the drug (without findings of congestive heart failure or progressive tumor) or the development of pulmonary infiltrates seen on x-ray studies in the absence of clinical findings on chest examination. Whenever any signs of lung toxicity appeared, the bleomycin therapy was discontinued and antibiotics and steroids were given. In about half the patients (46 percent) in whom early lung toxicity was noted on physical examination, the physical findings regressed over one to two months after stopping bleomycin therapy. Abnormalities on x-ray studies did not develop in this group. In the other half (54 percent), early radiographic evidence of interstitial abnormalities developed within two weeks of first recognition of changes on physical examination despite immediate discontinuation of therapy with the drug. These findings did in most instances regress with time.

Dose dependence of bleomycin pulmonary toxicity has been examined extensively. Blum and co-workers[37] analyzed the cases of 808 patients from several different studies and found risk of pulmonary toxicity to increase rapidly above a total dose of 450 mg. However, characteristic lung toxicity has been seen at all dose levels, even below total doses of 50 mg in some situations.[37] The four cases of bleomycin toxicity in Rudders' series involved total doses between 210 and 300 mg.[35] DeLena and associates[36] noted 33 percent and 48 percent incidence of pulmonary toxicity in two separate series with mean toxic doses of 132 and 135 mg per M^2 respectively. They suggested frequent careful physical examinations to detect early toxicity in all patients receiving greater than 100 mg per M^2 total dose of bleomycin. Schedule dependent pulmonary toxicity (that is, high dose intermittent versus low dose daily versus infusion) has not yet been clearly shown in the literature, but DeLena has suggested that high single doses or prolonged daily administration is particularly hazardous. No change in frequency of pulmonary toxicity with ages up to 70 years old was noted by Blum[37] or Haas.[38]

The response of the pulmonary parenchyma to a wide variety of toxic insults appears to move in a fairly stereotyped progression. It is possible to show both an alveolar and an interstitial component. Reactions to alkylating agents and bleomycin conform to this model. Alveolar air spaces are lined by type I (membranous) and type II (granular) pneumocytes. These latter cells normally produce surfactant. They contain characteristic "lamellar bodies" and are easily recognized on light or electron microscopy. In response to toxic pulmonary insults, there is a decrease in number of the type I pneumocytes and hyperplasia with metaplasia of the type II cells. With continued noxious stimulation, many type II cells are shed into the intraalveolar spaces. These cells disintegrate, inducing a serofibrinous reaction, and intraalveolar material accumulates in a fashion similar to pulmonary alveolar proteinosis. Interstitial edema develops, and reticulin and mature collagen deposition takes place in the alveo-

lar septae. In time the organized alveolar masses are incorporated into the thickened alveolar walls producing extensive fibrosis.[28,39-42]

The sequential nature of this process may explain the variable response to steroid therapy. The condition of those patients treated early during the exudative phase may improve with steroid therapy[18] plus discontinuation of the offending agent. When further organization has occurred, the process is essentially irreversible, and progressive respiratory insufficiency with restrictive ventilatory defects are the rule despite steroid use.

In nearly all the toxic reactions discussed thus far, the drug implicated in the pulmonary process has been used either alone or in combination with other chemotherapeutic agents not known to produce lung disease (for example, MOPP). Several new protocol studies combine alkylator therapy with methotrexate or bleomycin, or both. The question of whether or not significantly increased incidence of pulmonary toxicity will follow from such combinations has not yet been answered. However, a recent paper by Stutz and co-workers[43] concerning a five drug regimen for breast carcinoma suggests that some increase in pulmonary toxicity may occur with such combinations. This paper reviewed the courses of 17 patients with breast cancer treated with combination chemotherapy that included Cytoxan and methotrexate. In six, noninfectious pulmonary complications developed thought to be drug related based on timing, appearance and response to steroids. The 35 percent incidence was alarmingly high, and the authors speculated on the role of combined Cytoxan and methotrexate administration as an explanation for the high rate of pulmonary complication.

Recent experience of Einhorn and associates[44] suggests that the combination of bleomycin with radiotherapy may cause an acceleration of the fibrotic pulmonary reaction seen with either agent used alone. They treated 13 patients with oat cell carcinoma using combination chemotherapy including bleomycin, adriamycin, cyclophosphamide and vincristine, as well as 4,000 rads midplane tumor dose given in ten treatment fractions (five treatments, days 22 through 26 and five treatments, days 43 through 47) to the primary lung tumor. In five patients biopsy proven generalized interstitial pulmonary fibrosis developed. This appeared within two to six weeks of completion of the bleomycin therapy, which consisted of a total of 90 mg of drug given as 15 mg intravenously each week for six doses. The pulmonary injury was widespread and severe with three patients dying of respiratory failure and the two others limited by serious respiratory insufficiency. This frequency of major pulmonary fibrosis, especially after only 90 mg of bleomycin, is alarmingly high and appears to represent a serious synergistic toxicity of bleomycin and concommitant pulmonary parenchymal irradiation. Since this synergistic toxicity was recognized, an additional group of 20 patients has been treated by Einhorn and co-workers using the same treatment protocol except for the elimination of bleomycin. No further cases of generalized fibrosis have been noted.

Summary

The pulmonary parenchyma and pleural spaces are often sites of involvement with malignant disease. In addition, opportunistic infections often present as rapidly progressive pneumonitis in patients with malignant disease. Aggressive diagnostic maneuvers to differentiate these two categories of disease are appropriate. Several antitumor agents may cause pulmonary disease as well and such reactions must be considered in the differential diagnosis of progressive pulmonary infiltrates in patients with cancer in whom chemotherapy is being carried out. Many of these toxic or hypersensitivity reactions may seriously compromise the patients' clinical status. Long-term morbidity or mortality may result. Early intervention with steroid therapy appears to have a role in control of some of these reactions. Prospective awareness of such potential toxicities may help to avoid or minimize the severity of the pulmonary injury.

Addendum

Since submission of this manuscript, Holoye and co-workers[45] have reported the case of a patient treated with long-term intermittent BCNU therapy (treatment with nitrosoureas) for more than three years in whom there developed a syndrome of dry cough, dyspnea on exertion, and mild hypoxemia (Po_2 on room air). Lung tissue showed alveolar septal thickening with fibrous connective tissue and no inflammatory reaction. There was hyperplasia of type II alveolar lining cells. Patients are rarely treated with nitrosoureas over such a prolonged period of time. However, based on this report, it appears that long-term

intermittent nitrosourea therapy may be associated with lung toxicity in the form of pulmonary fibrosis. Since nitrosoureas are thought to act through an alkylating mechanism, the potential for nitrosoureas to produce such lung toxicity should not be completely unexpected.

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Peripheral Nerve Entrapments

A disruption in the function of a peripheral nerve results in a pattern of symptoms and signs that usually identifies the location and, at times, the nature of the pathological condition. A common type of neuropathy, the so-called entrapment neuropathy, is caused by compression on an intact nerve, thereby altering its conductivity. Entrapment of the median nerve at the wrist (the carpal tunnel syndrome) is the most common of the various entrapment syndromes that produce motor, sensory and autonomic symptoms. Damage to the nerve's myelin sheath results in delayed nerve conduction that can be measured by sensitive electrodiagnostic methods. Some diseases lead to nerve entrapments because they produce space-occupying lesions. For example, compression may be caused by rheumatoid synovitis, amyloid deposits or the interstitial infiltration produced by myxedema. Conservative management with aggressive treatment of any underlying disease should be instituted promptly. Operative decompression can usually be done easily in most entrapments and should be done before irreversible nerve damage occurs.

ANDREA CRACCHIOLO III, MD:* *The peripheral nerves of the body are numerous and usually traverse well-defined paths in the extremities. Because of their location, these nerves may become injured. When the injury occurs at a specific location, as result of either an aberration of anatomy or mechanical irritation, the condition is called peripheral entrapment neuropathy. Although such entrapments occur frequently, they are not easily identified or diagnosed.*

Peripheral nerve entrapments have been recognized for some time. In 1853 Paget[1] discussed median nerve compression caused by trauma, and Erb in 1876 commented on the greater susceptibility of motor nerves to external pressures. Hunt,[2] in 1908, first drew attention to peripheral compression of the median and ulnar nerves as a cause of paralysis of the intrinsic muscles. The first postmortem examination that showed the median nerve compressed at the wrist was carried out by Marie and Foix in 1913.[3] Sir Richard Learmonth[4] is credited with being the first surgeon to operate (in 1930) specifically for the purpose of decompressing the median nerve by transsecting the transverse carpal ligament.

In this symposium we shall focus primarily on the diagnosis of peripheral entrapment neuropathies, the pathophysiology of this process, the various medical diseases that can produce nerve entrapments and, to some extent, the treatment of this condition.

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Entrapment Syndromes

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AN ENTRAPMENT NEUROPATHY is a nerve lesion caused by pressure or mechanical irritation from some anatomical structures next to the nerve. This occurs frequently where the nerve passes through a fibro-osseous canal and is relatively fixed, but it can also occur as a consequence of impingement by an anatomical structure, such as bone, muscle or a fibrous band. Any mechanical injury of the nerve, therefore, could be considered a compression or entrapment neuropathy. This would include intervertebral disc protrusions impinging on nerve roots. In this review, however, we shall not include the radiculopathies and most plexus lesions, although these entities are often considered in the differential diagnosis of a peripheral nerve lesion. This situation is further complicated by the fact that proximal injury frequently coexists with peripheral entrapments and, indeed, may play a critical role in precipitating symptoms from a more peripheral site.

Peripheral nerves are classified as motor, sensory or mixed, depending on their function. The motor fibers arise from neurons in the anterior horn of the spinal cord, whereas sensory fibers arise from cell bodies in ganglia outside of the spinal cord. When the spinal roots leave the vertebral foramina, they are joined into a single nerve trunk within the dura of the spinal cord that is continuous with the epineurium, a condensation of collagen or connective tissue encasing the nerve. Within each nerve trunk there are collagen fibrils forming the perineurium that surrounds a collection of fibers called a fascicle. In the fascicle, there are thin slips of collagen, the endoneurium, that separate individual nerve fibers. This fascicular arrangement is especially important in pressure neuropathies, where there is a tendency for fascicular injury. That is, one fascicle may be injured while an adjoining one may completely escape the effects of the localized pressure.

Entrapment Signs and Symptoms

Pain is the most common clinical characteristic of an entrapment neuropathy. It can occur at the site of injury or can be distributed along the specific peripheral nerve involved. Paresthesias in the form of numbness, tingling, or crawling sensations in the distribution of the nerve may also occur. In addition, weakness of muscles innervated by a nerve distal to the point of injury may occur later. Similarly, atrophy of muscle may be observed; it is, however, a late finding. When nerves are relatively superficial, one can sometimes palpate the trunk, especially in such places as the elbow. The nerve may feel thickened or bound down in scar tissue as a result of a localized entrapment. Because of a heightened degree of irritation, particularly at the point of entrapment, percussing the nerve may produce an electric tingling sensation known as a Tinel sign. As a corollary, the nerve may be tender. Although an obvious Tinel sign may not be present, palpation of the nerve may show tenderness on comparison with the same nerve on the opposite extremity.

TABLE 1.—*Upper Extremity Entrapments*

Nerve and Entrapment Site	*Syndrome*
Median	
Above elbow	Supracondylar
Proximal forearm	Pronator
Forearm	Anterior interosseous
Wrist	Carpal tunnel
Hand	Digital
Ulnar	
Thoracic outlet	Thoracic outlet
Elbow	Cubital tunnel
Hand	Proximal Guyon's tunnel
	Distal Guyon's tunnel
	Terminal motor
Finger	Digital
Radial	
Axilla	Axilla
Humerus	Saturday night palsy
Forearm	Spinator
	Posterior interosseous
	Superficial cutaneous

Median Nerve

Table 1 lists several median nerve entrapment syndromes. The most common is the carpal tunnel syndrome, where the median nerve is entrapped beneath the transverse carpal ligament (Figure 1).[5] A lesion at this point produces painful paresthesias, frequently nocturnal, which can be severe enough to awaken the patient with pain. Wrist percussion often produces a Tinel sign. Ultimately, constant paresthesias developed in the palmar surface of the thumb, index finger, and middle finger, and half of the ring finger. This sensory impairment often extends to the dorsal surface of the fingertips. There is usually no

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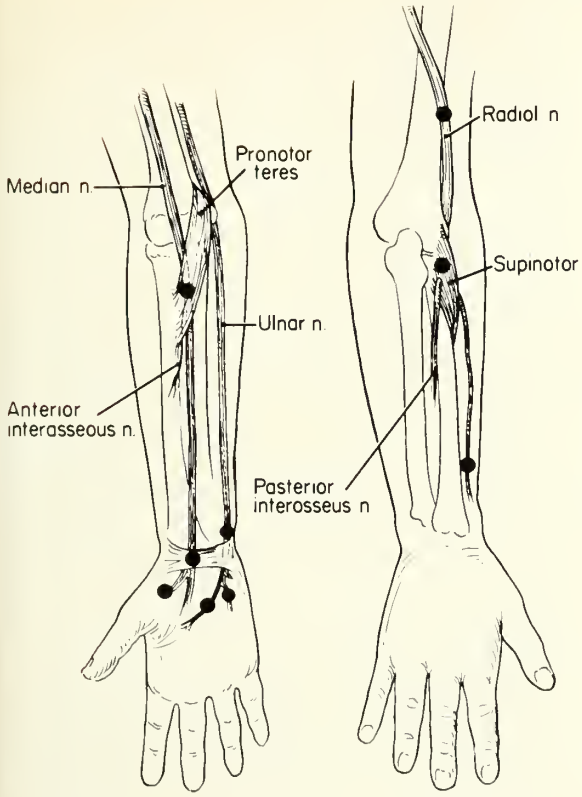

Figure 1.—Upper extremity, volar side (**left**) and dorsal side (**right**), showing the course of the median, ulnar and radial nerves. Entrapment points (**circles**) include the median nerve entrapment at the elbow and wrist (carpal tunnel); the ulnar nerve at the elbow, where it may become entrapped behind the median epicondyle and at the wrist; the radial nerve entrapment at the elbow, the midarm and the distal sensory branch proximal to the wrist.

sensory impairment over the proximal palm because this region is supplied by a branch of the median nerve that arises before the carpal ligament and thereby escapes entrapment. Subsequently, weakness of the thenar muscles occurs. The main muscle involved is the abductor pollicis brevis, but the opponens pollicis is also frequently affected. Atrophy of the thenar muscles may eventually occur as a consequence of continued entrapment.

The pronator syndrome is caused by entrapment of the median nerve as it passes through the pronator muscle (Figure 1).[6] The clinical history usually includes poorly localized forearm pain, but on occasion the patient may complain of paresthesias in the digits. It may be quite difficult to differentiate between the pronator syndrome and a carpal-tunnel syndrome. Pain is usually more proximal in the pronator syndrome and an electromyogram may show denervation in the pronator muscle.

The anterior interosseous nerve is a motor branch of the median nerve (Figure 1).[7] As it passes over the anterior interosseous membrane, it can become entrapped and produce weakness of the flexor pollicis longus and flexor digitorum profundis muscles. Testing the strength of these muscles will aid in the diagnosis; however, the absence of sensory symptoms should be a clue to this condition.

In about 1 percent of upper extremities, there is a supracondylar process that is an anomalous bony spur found a few centimeters above the medial epicondyle. A ligament of Struthers may be present connecting this spur to the medial epicondyle, the median nerve passing underneath.[7] Although this is usually an asymptomatic variant, median nerve entrapment may (rarely) occur in this area, particularly if there has been localized trauma.

Ulnar Nerve

The ulnar nerve may be involved in a scalenus anticus or cervical rib syndrome. In this syndrome, the lowermost portion of the brachial plexus may be affected. Inasmuch as the ulnar nerve is made up of fibers from the lowermost cervical roots, this is the nerve most affected. The symptoms are: (1) paresthesias in an apparent ulnar distribution along the ulnar surface of the forearm, encompassing the fifth finger and the ulnar half of the ring finger, (2) weakness of the intrinsic muscles of the hand innervated by the ulnar nerve and (3) pain, primarily in the shoulder or thoracic region.

The most common site of ulnar entrapment is probably at the elbow within the cubital tunnel.[8,9] The floor of this tunnel is the medial ligament of the elbow, and the roof is formed by an aponeurosis between the olecranon and the medial epicondyle. The symptoms are atrophy of the intrinsic muscles of the hand and forearm (the flexor carpi ulnaris and the ulnar head of the flexor digitorum profundus muscle); sensory impairment is in an ulnar distribution.

At least five variations of motor and sensory impairment have been described in the hand.[10] In this report we shall consider only three syndromes affecting the ulnar nerve (Figure 1).[11] A lesion at the wrist will cause pain and weakness of all ulnar innervated muscles. There is also sensory loss in a distal ulnar distribution. At the

pisohamate tunnel all ulnar innervated hand muscles are affected. There is, however, no sensory loss, as the nerve supplying the skin originates proximal to the tunnel. Finally, injury to the distal or terminal motor branch causes weakness and atrophy of the adductor pollicis and the medial two lumbricles. The hypothenar muscles are spared and there is no sensory loss. The latter two syndromes are frequently associated with trauma to the palm or hand—as in the case of bicycle riders and persons using canes or heavy, vibrating hand tools.[12]

Finally, the digital nerves from the median or ulnar nerves may be entrapped in the intermetacarpal tunnel, especially if the finger is hyperextended or if there is direct injury to the area. This condition is usually easy to diagnose because of the characteristic sensory distribution of the digital nerves and the lack of muscle weakness.[13]

Radial Nerve

The radial nerve arises as an extension of the posterior trunk of the brachial plexus. Once past the axilla, the nerve winds around the humerus in the spiral groove where it virtually lies on the bone, making it highly susceptible to pressure injury in the area (Figure 1). The nerve then moves anteriorly below the insertion of the deltoid and lies deeper within the extensor muscles of the forearm. Subsequently, the nerve divides into two branches, each of which may become injured in a separate entrapment syndrome. The two branches are the deep motor branch (or posterior interosseous nerve) and a superficial cutaneous branch which supplies the dorsum of the thumb and hand.

Injury to the nerve in the axilla would cause weakness of the triceps, the wrist and finger extensors, thereby resulting in a wrist drop. There would also be weakness of forearm supination, along with paresthesias in the dorsum of the thumb and the web between the thumb and index finger. Axillary lesions are usually caused by trauma such as the incorrect use of crutches.

The radial nerve can easily be compressed as it winds around the humerus and at this level the triceps is usually spared. The posterior cutaneous nerve of the forearm is frequently affected, however, and this produces paresthesias extending from the extensor surface of the forearm to the hand. Typically, injury in this area may be due to a person falling asleep with his arm over a chair, the well-known "Saturday night palsy" or "lover's palsy."

Compression of the radial nerve laterally, just before the posterior interosseous nerve pierces the supinator muscle, can produce a syndrome of weakness of the supinator and the finger extensors. As the wrist extensors arise before this point, their function may be preserved, although the wrist may tend to deviate in a radial direction. There will be no sensory loss and brachioradialis function will be intact. Injury to the posterior interosseous nerve at the supinator muscle is caused by soft tissue injury, tumor and occasionally subluxation of the radial head.[14]

Finally, injury to the most terminal cutaneous branch of the radial nerve results in pain and paresthesias in a radial distribution. Such injury may be caused by casts, tight bracelets or watch bands.

Suprascapular Nerve

Suprascapular nerve entrapment is a rare occurrence. This nerve, which is a branch of the upper trunk of the brachial plexus, passes through the suprascapular notch under the transverse scapular ligament to innervate the supraspinatus and infraspinatus muscles. Traction or pressure on the nerve can cause irritation in the region of the suprascapular notch. It may also produce poorly localized pain in the posterior aspect of the shoulder, and occasionally atrophy of the supraspinatus and infraspinatus muscles. Repeated cross adduction of the arm, such as by pitching or throwing motions, may traumatize the nerve.[13]

Axillary Nerve

The axillary nerve is rarely encountered in an entrapment syndrome. Recently, however, attention has been focused on the quadralateral space through which the auxillary nerve passes and then winds behind the humerus to supply the deltoid muscle. This nerve may be injured during dislocations of the shoulder and fractures of the head of the humerus. Painful atrophy of the deltoid, however, may occur without associated trauma, which is perhaps related to entrapment within the quadralateral space.

Lateral Femoral Cutaneous Nerve

The lateral femoral cutaneous nerve is derived from the L2 and L3 lumbar roots. This nerve passes from the lateral border of the psoas muscle

and runs laterally around the pelvis. It then passes through an opening formed by the attachment of the inguinal ligament to the anterior superior iliac spine. About 10 cm below the anterior superior iliac spine the nerve divides into an anterior and a posterior branch. The anterior branch passes to the skin of the anterior lateral aspect of the thigh and the posterior branch innervates the skin over the lateral and posterior portion of the thigh. This is a sensory nerve without any motor function and, therefore, only sensory symptoms will be present.[15] The entrapment occurs as the nerve passes through the inguinal ligament in close proximity to the bone. Compression at this point causes burning paresthesias, known as meralgia paresthetica. The area is hypersensitive to touch and examination usually shows altered sensation over the lateral aspect of the thigh. The mechanical cause of injury is traction or pressure in the region of the ligament, frequently occurring in persons who wear tight, constricting garments or belts. This syndrome is often seen in obese persons who have a lax abdominal wall. Surgical trauma may also produce symptoms.

Femoral Nerve

The femoral nerve is derived from the second, third and fourth lumbar roots. This nerve passes along the floor of the pelvis lateral to the psoas muscle, then joins the femoral vessels under the inguinal ligament. The medial and intermedial cultaneous nerves of the thigh are derived from the femoral nerve. Distally, the nerve becomes the saphenous nerve, which supplies sensation to the medial aspect of the leg. Femoral nerve compression at the groin may be related to an inguinal hernia or to injury after surgical treatment of hernia. One may find lesions of the femoral nerve after careless retraction during surgical operation on the abdomen. Occasionally, this nerve may become injured as a result of retroperitoneal or intrapsoas hemorrhage in persons who are receiving anticoagulants or who have a bleeding disorder.[16] Injury to the saphenous nerve may be caused by improper positioning during pelvic procedures and after saphenous vein stripping.

Obturator Nerve

The obturator nerve also originates from the second, third and fourth lumbar roots, and passes along the floor of the pelvis before traveling through the obturator canal with the obturator vessels. The obturator nerve supplies the adductor magnus, longus, and brevis muscles as well as the gracilis. In addition, it also supplies sensation to the upper medial portion of the thigh. Injury to this nerve as it passes through the canal causes pain in the groin, extending along the medial aspect of the thigh, and may produce sensory impairment in the appropriate distribution. Lesions of the obturator nerve are rare and usually occur after surgical procedures on the pelvis or following difficult labor.

Sciatic Nerve

The sciatic nerve originates from the L4-S1 nerve roots and is formed from the lumbosacral plexus. The nerve leaves the pelvis through the sciatic notch and has two major divisions, the tibial and common peroneal. The sciatic nerve is deeply placed and is not usually involved in a pressure neuropathy. This nerve can be injured, however, primarily in the region of the sciatic notch. Thin persons who have pressure applied to this area for a prolonged time are especially susceptible to this type of injury.

Ordinarily, the sciatic nerve is involved in a pressure syndrome after it separates to form its two branches, the common peroneal and posterior tibial nerves. The common peroneal nerve winds around the head of the fibula and then divides into two branches, the deep peroneal and the superficial peroneal nerves. The deep peroneal nerve supplies the tibialis anterior, extensor hallucis longus, extensor digitorum longus, peroneus tertius, and the extensor digitorum brevis along with the second dorsal interosseous muscle. A cutaneous branch that arises distally supplies the skin between the great toe and the second toe. The superficial peroneal nerve supplies the peroneus longus and brevis muscles; it also supplies sensation to the skin over the remaining portion of the great toe and the dorsum of the foot.[11]

Common peroneal nerve compression can occur at the fibular head from any form of pressure on the side of the leg. This syndrome has been produced by habitual sitting with one leg crossed, as well as by sleeping on a firm surface. Because of its relatively superficial location, the nerve can also be injured by improperly applied casts or tight boots. Injury to the common peroneal nerve produces a foot drop and an inability to evert the foot. There is also sensory loss over the dorsum of the foot.

Occasionally there may be selective involve-

ment of the deep peroneal or superficial peroneal nerves. In deep peroneal nerve injury there is only a sensory loss limited to the region immediately between the great and second toe. On the other hand, a superficial peroneal nerve injury would have no effect on the patient's ability to dorsiflex his foot; sensory loss would be over a wider area and the selective movement of eversion would be impaired.

A deep peroneal entrapment syndrome has been described in the foot. Trauma to the dorsum of the foot can easily injure this nerve because it is relatively superficial in this area. There is a passage, the so-called anterior tarsal tunnel, on the dorsum of the foot, roofed over by the inferior extensor retinaculum. Compression neuropathy of this nerve at the ankle may be manifested by wasting of the extensor digitorum brevis muscle and loss of sensation over the web between the great and second toes.

Posterior tibial nerve compression is rare in the popliteal fossa. The nerve, however, may be entrapped in the region of the ankle, the well-known tarsal tunnel syndrome.[11,13] The tarsal tunnel is an osteofibrous pathway with a roof composed of the flexor retinaculum. In addition to the posterior tibial nerve there are numerous structures in this tunnel. These include the tendons of the flexor digitorum longus, flexor hallucis longus and posterior tibial muscles. The posterior tibial vessels are also present. Mechanisms of compression are associated with a tenosynovitis, venous engorgement, osteoarthritis, acute trauma and posttraumatic deformities. The most common complaints with this syndrome are pain and burning paresthesias, usually confined to the sole of the foot. There may be more specific involvement of the medial or lateral plantar nerve, producing specific sensory impairment. Patients rarely complain of motor loss, although atrophy and weakness may be present.

The most distal branch of the posterior tibial nerve may also become injured by poor foot posture, prolonged standing on sharp edges or exercise not done ordinarily, such as barefoot running. The diagnosis depends on a complaint of painful paresthesias of the foot, weakness and atrophy of the intrinsic muscles of the foot, and frequently a history of unusual trauma.

The critical factor for arriving at a diagnosis of any nerve entrapment is the recognition of the involvement of a single peripheral nerve rather than several, which would imply a more proximal or perhaps root level or plexus level lesion. A summary of entrapment neuropathies would not be complete, however, without including the potential of combined entrapments producing peripheral symptoms. This would involve nerve injury at more than one level, thereby producing symptoms referable to only the more distal entrapment. This is most frequently seen in patients with an apparent carpal tunnel syndrome who on examination also show evidence of a more proximal lesion. In this regard, the clinical history is of great importance. The patient may complain of neck or shoulder pain and have vague sensory symptoms above the level of the wrist. In addition, there may be prominent symptoms of an apparent carpal tunnel syndrome. It is not unusual for an electromyogram to show a cervical radiculitis, or the results of nerve conduction studies may suggest a thoracic outlet syndrome, even though the patient's primary physical complaints and findings are in a distal median nerve distribution. This is called a combined entrapment syndrome and it may occur in a high percentage of peripheral entrapments.

Pathophysiology and Electrodiagnosis

DAVID S. CAMPION, MD*

In order to understand the process of peripheral entrapment neuropathies, it is important to know the pathophysiology of nerve entrapment and to appreciate electrodiagnostic techniques that determine nerve damage.

The basic element in the neuron is the nerve fiber or axon, which has a dual function. First, a membrane potential of some 90 mV exists across the axon membrane, the axolemma, and this provides the force by which an action potential can travel down the axon. Second, trophic substances produced in the cell body are constantly flowing down the axon at about 41 cm per day; they have profound effects on both the electrophysiological properties of the axon and on the functioning of the end organ. In motor fibers and in many sensory fibers, the axon is

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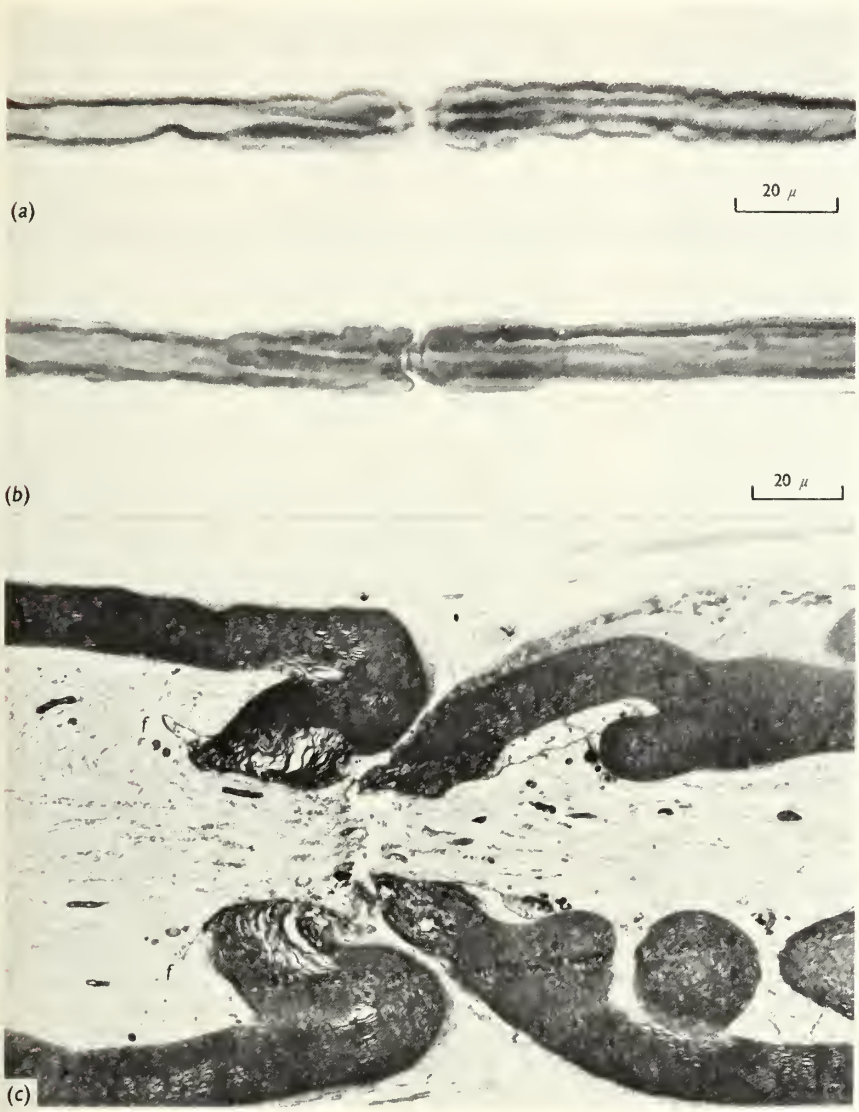

Figure 2.— a, Normal node of Ranvier with a nodal gap 1.2μ wide. **b,** Abnormal node of Ranvier, four days after compression; there is minimal invagination of the paranode on the left by the one on the right, with obliteration of the nodal gap. **c,** Low-power electron micrograph of node shown in **b;** the axolemma of the invaginated paranode shows redundant folds (f); the discontinuity of nodal axoplasm is due to artifact. (Reduced from magnification × 4900.) From Ochoa, Fowler, and Gilliatt,[18] reproduced with permission from the *Journal of Anatomy.*

ensheathed by a Schwann cell, whose cell membrane has become specialized and has wrapped itself around the axon, giving the axon a covering of myelin. This myelin sheath is an electrical insulating material that encloses the entire length of the axon, except for the nodes of Ranvier where there is an interruption of the myelin sheath. Nodes occur at intervals of 0.1 mm in smaller fibers and 1.8 mm in larger fibers; the region between the nodes is called the internode.

The presence of myelin is of tremendous physiological importance, because only at the nodes is the permeability of the axon membrane able to be altered by current flowing from a neighboring node. The action potential, or nerve action potential, can be considered as jumping from one node to the next; this process is called saltatory conduction.[17] Therefore, the velocity of the nerve action potential is increased from 1 to 4 meters per second in muscle or unmyelinated nerve to about 40 to 70 meters per second in a myelinated nerve. This specialization, however, has its hazards. If the myelin is lost, then no action potential can move down through the demyelinated segment, and a conduction block ensues. If the distance between nodes is shortened, as occurs with demyelinization followed by remyelinization, then slower conduction occurs.

Anatomically, after an acute compression (for example, "Saturday night palsy" of the radial nerve), a displacement of the nodes of Ranvier occurs away from the site of compression (Figure 2).[18] The node is actually pushed into the next internode, a few microns in mild cases, but as

much as 300 microns in severe cases. With only a slight displacement of the node, there is damage to the myelin, resulting in delayed activation by the nerve action potential, and a slight slowing of conduction through the damaged area. This may be difficult to detect unless a large number of fibers are affected. With greater displacement of the node, the normal gap at the node of Ranvier is obliterated. There is, therefore, an intact axon, but one in which the nodal gaps are completely covered, thereby blocking conduction. No muscle response is seen with proximal stimulation. However, if such a nerve is stimulated distal to the injured side, then a normal action potential travels down the axon and a normal muscle response occurs. This injury, known as neurapraxia or physiological block, takes hours to weeks to recover. The duration of the compression and the area of nerve compressed determines the time the conduction block will persist.[19] There is never any actual denervation of the muscle and therefore no fibrillation potentials—the common electromyographic indication of denervation. Recovery from physiological block is complete.

Prolonged pressure results in a severely damaged fiber with partial or complete rupture of the myelin lammellae in the invaginated area. After two to three days, disintegration and removal of the damaged paranodal myelin occurs, and a section of demyelinated nerve is exposed. During a period of one to three months, the axon remyelinates, but with a shortened internode, and consequently a slowing of conduction through the section of remyelinated nerve. Severe pressure may cause a pronounced invagination of the internode, leading to the rupture of the myelin sheath and damage to the axolemma itself. If the axon is damaged, then a breakdown of the axons begins, the so-called Wallerian degeneration. Initially in Wallerian degeneration there is an increase in the number of Schmidt-Lanterman clefts, segmentation of myelin into ovoids, and an increase in Schwann cell lysosomal activity with phagocytosis of the myelin ovoids into the Schwann cells. Death of the axon at the site of compression leads to the death of the axon distally; as the axon dies, its myelin—which is dependent on an intact axon for its survival—disintegrates distally. Finally, all that remains are Schwann tubes, into which the axon can grow back at a later date. Because the axon itself is damaged in Wallerian degeneration, there is a blocking of conduction at the site of the injury.

Extensive nerve conduction studies of a patient with Wallerian degeneration would show the following sequence of events: Proximal stimulation would block conduction through the compressed area. Stimulation distal to the compressed area would show for the first 24 hours a normal nerve and normal muscle action potential response. During the following four days, however, the nerve action potential and muscle response would steadily decrease in size; the response would depend on the number of axons damaged. If the total nerve had been destroyed, there would be no muscle contraction. If 50 percent of the motor axons had been destroyed, then approximately 50 percent of a normal muscle contraction would occur. In addition to the electrical block, there would be blockage of trophic substances coming down the nerve. After 10 to 20 days, the muscle would become irritable, and positive sharp waves and fibrillation potentials (indicating denervation of the muscle) would appear. With both mildly and severely damaged axons, there would usually be slowing of conduction through the site of injury, a diminished motor response and a variable number of fibrillation potentials.

If such a patient is followed, and the axons grow back down the Schwann tubes (at about 1 to 4 mm per day), then with reinnervation the fibrillation potentials diminish, new motor unit potentials appear, and finally the muscle response returns. Reinnervation involves new groups of muscle cells; this is reflected in an electromyogram by the presence of long, complex, often large, motor unit potentials. Conduction velocity down the nerve would initially be very slow, but both conduction velocity and muscle response can continue to improve 24 months after an injury; there is usually no further improvement in the third year. The final response of the speed of conduction down the nerve is never more than 75 to 80 percent of normal.

Such a reinnervated nerve is composed of thinly myelinated axons with short internodes, instead of the usual thickly myelinated axons. Moreover, entrapment affects the large nerves more than the small nerves, for which there are two possible explanations. First, according to the LaPlace law, for a given pressure the tension in the wall of the larger fibers is more than the tension in the smaller fibers. Therefore, damage to the myelin is more likely to occur in the large fibers. Another possible explanation may be that the axon in the larger fibers is considerably narrowed at the nodes

TABLE 2.—*Nerve Conduction Studies—Carpal Tunnel Syndrome: Sequence of Electrodiagnostic Abnormalities Observed in the Median Nerve as Symptoms Develop*

Severity	*Abnormalities*
mild	Sensory potential amplitude decreases
	Sensory latency is prolonged (normal: 3.7 msec or less)
moderate	Motor potential amplitude decreases
	Motor latency is prolonged (normal: 4.6 msec or less)
	Conduction velocity decreases (normal: 49 m/sec or faster)
severe	Needle examination of abductor pollicis and opponens pollicis shows denervation potentials

of Ranvier but expands again in the internodes. A pressure gradient along the axoplasm would therefore reach a resistance at the node of Ranvier and push the node of Ranvier into the adjacent internode. Because there is no such narrowing of the axon at the node of Ranvier in the smaller axons, these are protected from damage under pressure.

In a chronic entrapment, such as a carpal tunnel syndrome, the internodes of the myelinated fibers taper at the end near the entrapment, and are swollen at the end away from the entrapment.[20] What has happened is that there has been a movement of myelin lamellae relative to the axon, the direction of slippage being away from the site of entrapment. The thin end of the internode is towards the area of pressure and the thick end is away from it; the myelin lamellae are looped and folded back on each other. With chronic or more severe pressure, demyelinization occurs, and finally remyelinization, so that shorter internodes are seen, and again a slowing of conduction when compared with normal. Less frequently than in acute compression, there is Wallerian degeneration with denervation of the muscle.

In a patient with a carpal tunnel syndrome (probably the commonest form of entrapment) a nerve conduction study should always include a bilateral determination of motor and sensory distal latencies of the median and ulnar nerves. Such bilateral measurement is necessary because it is not unusual to find early signs of carpal tunnel syndrome on the unaffected side. In addition to distal latencies, the conduction velocity of the median nerve should be measured. Needle examination of both upper extremities and cervical paraspinal muscles should be undertaken to rule out a concomitant abnormality such as a radiculopathy. The sequence of electrodiagnostic abnormalities in carpal tunnel syndrome is listed in Table 2. The determination of the median nerve sensory latency is important, as its prolongation is the earliest reliable sign of median nerve entrapment. Prolonged motor latency and denervation indicate very severe entrapment. Inasmuch as entrapment at any site is more likely to occur if an underlying neuropathy is present, such as diabetic neuropathy, prolongation of the ulnar nerve latencies can serve as the indication of the possible presence of an underlying neuropathic process.

TABLE 3.—*Factors Influencing the Development of Peripheral Nerve Entrapment*

A. The superficial and susceptible nerve
- Ulnar nerve at elbow
- Radial nerve at axilla
- Peroneal nerve at knee
- Hereditary susceptibility to pressure palsies

B. The potentially confined peripheral nerve
- Median nerve at wrist (carpal tunnel syndrome)
- Ulnar nerve at wrist
- Deep radial nerve at elbow
- Tarsal nerve at ankle

C. The expanded peripheral nerve
- Edema
  - Hypothyroidism
  - Acromegaly
- Familial amyloid
- Chronic hypertrophic neuropathy
- Leprosy

Medical Causes of Nerve Entrapment

RODNEY BLUESTONE, MB, MRCP*

THERE ARE two situations that readily permit entrapment of a peripheral nerve. The first of these has been discussed by Dr. Namerow and occurs when the peripheral nerve passes through a shallow groove or over an exposed area, and

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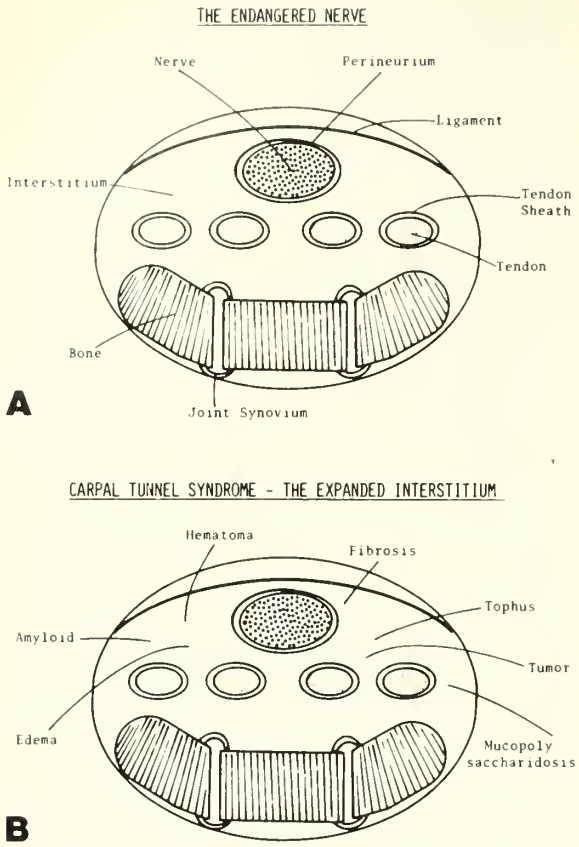

Figure 3.— A, Schematic representation of the median nerve lying in the carpal tunnel, showing the various structures in proximity to the nerve. **B,** Schematic representation of the median nerve lying within the carpal tunnel; various pathologic processes within the interstitium that may result in carpal tunnel syndrome are indicated.

is therefore susceptible to trauma. Examples of this mechanism are very important and fortunately rather easy to diagnose (Table 3A). They include ulnar nerve compression at the elbow after severe bony or soft tissue injury; the classical "Saturday night palsy" of the radial nerve; peroneal palsy from falling asleep in the cross-legged position, and the condition in those rare patients who have a peculiar hereditary susceptibility to pressure palsies in general. The second situation predisposing to entrapment occurs when the peripheral nerve passes through a potentially confined space (Table 3B). Under those circumstances any pathologic alteration within the space may result in nerve compression.

Entrapment of the peripheral nerve within a confined space may be a local manifestation of a more generalized disease and therefore becomes an important focal point for the internist. The most common site where compression may occur is at the median nerve in the wrist.[13] Less frequently, similar mechanisms may result in entrapment of the ulnar nerve at the wrist,[21] of the deep radial nerve over the anterolateral aspect of the elbow joint[22] and of the posterior tibial nerve as it courses beneath the medial malleolus of the ankle joint.[23]

Carpal tunnel syndrome is a common, potentially disabling and usually curable disorder of great interest to internists, rheumatologists and neurologists. The carpal tunnel syndrome can be used as a prototype model for the way in which disease affecting the surrounding structures within a confined space may produce local peripheral nerve compression. When considering the various tissue components adjacent to and within this space, it is easy to see how a multitude of disorders, both localized and systemic, can result in median nerve entrapment (Figure 3A). This entrapment may arise as a result of direct nerve compression, or perhaps as a result of a nonspecific increase in tissue pressure within the confined space.

Diseases of the bony components, such as a displaced fracture or gross osteophytosis (secondary to degenerative joint disease) rarely result in median nerve compression. Usually the traumatic event is well-documented and the radiographic findings are sufficiently clear-cut for diagnosis. The synovial component of the confined space is an important potential cause of nerve damage; the synovial membrane lines the capsules of the multiple small joints of the carpus as well as the tendon sheaths as they course across the wrist joint. Rheumatoid arthritis, and to a lesser degree other rheumatoid-like disorders, may result in a greatly hypertrophied synovium that may become invasive and destructive ("pannus"). This synovial hypertrophy may readily increase the pressure within the carpal tunnel, resulting in any degree of median nerve compression. Frequently, the patient has a similar rheumatoid inflammation in the small joints of the hand along with the wasting of the muscles. It is important to ascertain whether impaired hand function in a patient with rheumatoid disease is the result of the rheumatoid process alone, or is partially due to a secondary carpal tunnel syndrome. Indeed, the incidence of significant median nerve compression in rheumatoid disease is much higher than simple symptomatology would suggest.[24] Electromyographic

studies of median nerve conduction in many patients with rheumatoid arthritis who have no clinical indication of carpal tunnel syndrome have shown a strikingly high incidence of subclinical nerve entrapment.

Diseases affecting the interstitial tissue component of the carpal tunnel may also produce nerve compression (Figure 3B). This interstitial component usually consists of loose connective tissue and fat, as well as the fibrous tissue sheaths surrounding tendons and nerves. Prolonged edema within this interstitial tissue can readily compress the median nerve. Transient edema is common during pregnancy, and the typical mild symptoms of median nerve compression rarely become severe enough to warrant treatment by the third trimester.[25] Perhaps the most common cause of persistent noninflammatory edema around the wrist is seen in elderly patients with frozen shoulders and shoulder-hand syndrome. The shoulder-hand syndrome usually follows myocardial infarction, pneumonia or relatively minor trauma in elderly patients; it is not unusual for the prolonged swelling of the immobile and dystrophic hand to result in secondary median nerve entrapment. Hypothyroidism may result in an excessive amount of myxedematous infiltration of the carpal tunnel interstitium; patients may present with symptoms of a carpal tunnel syndrome even before other gross evidence of myoedema is clinically apparent.[26] A similar situation is seen in patients with acromegaly, in whom mild acroparasthesiae is a common symptom.[27] Moreover, it is the most readily and dramatically reversible symptom of that endocrine disorder. Therefore, acromegalic patients treated by yttrium implant or hypophysectomy frequently notice relief of the numbness and tingling in their fingers within 24 hours after operation. Extraneous tissues rarely become deposited or develop within this interstitial tissue compartment. The best examples of this are seen in patients with amyloidosis, usually secondary to paraproteinemia, where part of the periarticular amyloid deposition may include the soft tissue spaces around the wrist joint.[28] This boggy periarticular swelling may mimic a primary arthropathy. In patients with various types of mucopolysaccharidosis, adequate infiltration of the carpal tunnel interstitial tissue may develop, resulting in clinically important nerve compression. This rare group of mucopolysaccharide disorders is actually one of the common causes of carpal tunnel syndrome seen in childhood.[29] Occasionally in patients with coagulopathies there may be blood loss into the carpal space and hematoma formation may result in median nerve compression. In patients with systemic sclerosis, enough ectopic collagen may be deposited around the wrist for nerve entrapment to develop. Last, various rare tumors within the carpal tunnel have been found, ranging from tophus formation in patients with chronic gout to the simple ganglion and lipoma. The latter tumor also causes compression of the deep radial nerve over the anterior aspect of the elbow.[30]

One of the common causes of median nerve entrapment is loss of resiliency and tightening of the superficial carpal ligament as it traverses anteriorly to the carpal compartment. This mechanism probably accounts for many patients who present with "idiopathic" carpal tunnel syndrome, a constriction readily relieved by surgical operation. Finally, the nerve may become expanded or altered, thereby resulting in undue vulnerability and constriction within an otherwise normal carpal space (Table 3C). The causes of peripheral nerve expansion are numerous and include hypothyroidism, acromegaly, familial amyloidosis, leprosy and chronic idiopathic hypertrophic neuropathy. Altered, and particularly susceptible, nerves are found in patients with diabetes mellitus and chronic renal failure.

The local disease processes discussed above, regardless of the underlying cause, may be aggravated by movement and trauma. Therefore, an attempt at the nonspecific medical management of carpal tunnel syndrome may be justified, regardless of the underlying cause. The medical management usually consists of splinting of the wrist joint in a slightly extended position, at least during the night, when external protection from undue flexion is most needed. In addition, physicians may inject a small quantity of corticosteroid within the carpal tunnel space, if a reversible edema or inflammation, or both, are contributing to the nerve entrapment. A small daily dose of oral diuretic may also improve symptoms. One should not, however, persevere too long with the medical management of carpal tunnel syndrome. If clinical and electrophysiologic response to splinting, diuretics or local corticosteroids is not immediately apparent, it is important to proceed to surgical decompression.

Surgical Treatment

ANDREA CRACCHIOLO, III, MD*

THE PRIMARY CONSIDERATION of any physician evaluating a patient with an entrapment neuropathy is to confirm the diagnosis and try to uncover the cause of the entrapment. As the clinical manifestations of a nerve entrapment may vary in severity, the patient's history and symptoms should be reviewed. Pain and paresthesias are the most frequent symptoms and may increase by certain positions of the extremity. Proximal radiation of pain (Velleix phenomenon) can occur, and vasospastic symptoms in the hands and feet have also been reported.[31] Percussion or compression of the nerve may produce symptoms and a careful neurologic examination, particularly of the nerve's motor function, will determine muscle weakness; hypersthesia, however, may be difficult to elicit.

The cause of the entrapment may initially be obscure. Patients with bilateral involvement, found most frequently in the carpal tunnel syndrome, may have a type of disease that produces the entrapment.[32] A complete medical evaluation of such patients is recommended; treatment of an underlying disease may control symptoms and thereby make surgical treatment unnecessary.

Local measures, such as immobilizing the wrist joint, may also be helpful in patients with carpal tunnel syndrome.[33] By using a simple plaster wrist splint, the wrist can be held in a neutral position. The splint should be worn continuously at night (this frequently relieves nocturnal symptoms) and intermittently or constantly during the day, as needed to control symptoms. The injection of medications, usually corticosteroid, around the entrapment should be done cautiously. The local effect of the medication may be helpful, but even a small amount of fluid could, by occupying some space, aggravate the nerve compression. Moreover, the medication could inadvertently be injected into the nerve itself, causing the patient additional severe pain and possibly injuring the nerve.

Nonoperative treatment should usually be on a trial basis, unless one of the following is noted: (1) severe unremitting symptoms, (2) significantly abnormal findings on nerve conduction studies, (3) muscle atrophy or weakness produced by the entrapment, (4) a condition that is not likely to respond to conservative treatment, such as a tumor or (5) failure of previous adequate nonoperative treatment.

If conservative care is not indicated, postponing an operation may indeed be unwise. Usually, the patients' symptoms are so unbearable that they will demand something to be done to provide relief. Occasionally, a patient will present with relatively minor sensory symptoms, but will display motor weakness and muscle atrophy. These patients should be carefully evaluated for the presence of a neuropathy, and if an entrapment syndrome is the cause, prompt operative decompression of the involved nerve should be carried out.

Operative decompression of any peripheral nerve should follow certain principles and techniques: (1) The exact anatomical site of entrapment must be carefully determined preoperatively. (2) A knowledge of the anatomy of the peripheral nerve at the entrapment site is essential, especially the location of branches that innervate adjacent muscles, so that they will not be inadvertently injured. (3) The operations should always be carried out in an operating room, even though the stay in hospital is short and at times only a few hours of outpatient observation is required. (4) Many surgeons prefer a general anesthetic, but block anesthesia is satisfactory and is preferable in some patients. (5) A pneumatic tourniquet should be used proximally to insure a bloodless field and allow excellent visualization of all structures. As most nerve decompressions require a short period of time, complications rarely occur secondary to the use of a tourniquet. (6) Adequate operative exposure should be provided by incisions of adequate length. (7) The nerve and adjacent structures should be handled with care. (8) The operation should thoroughly decompress the nerve; in certain cases, the nerve may require transposition to a more favorable area, so that further entrapment will not recur. (9) The entrapment site should be carefully inspected to insure that no pathologic condition remains undetected.

Compression of the median nerve at the wrist is by far the most common nerve entrapment syndrome. The median nerve passes across the volar side of the wrist through the carpal tunnel that is formed by the transverse carpal ligament covering the concavity of the carpal arch. The anatomic reason for the frequent involvement of this nerve is probably that there are so many other

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Figure 4.—Carpal tunnel syndrome in a patient with rheumatoid arthritis. Synovitis about the flexor tendons was the prominent pathological finding. In addition to compressing the median nerve, the synovitis ruptured several flexor tendons.

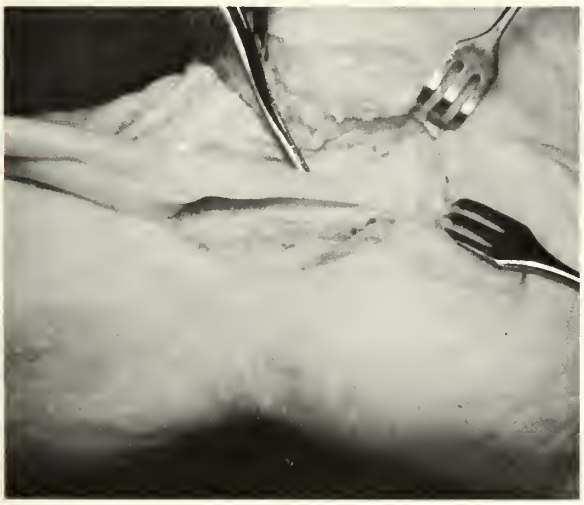

Figure 5.—Longitudinal incision across the volar aspect of the wrist exposing the median nerve. Note the pronounced "hourglass" compressions of the nerve.

structures within the carpal tunnel. All the flexor tendons to the fingers are in the carpel tunnel. Each of the nine tendons is covered with a tenosynovium, and any irritation of this synovium can produce a synovitis, which increases the contents of the carpal tunnel and thereby compresses the nerve (Figure 4). The presence of aberrant structures within the tunnel, such as blood vessels, muscle or a mass, can produce the same compressive effect. A longitudinal incision that exposes the entire nerve is strongly recommended (Figure 5). Short transverse incisions, although possibly giving better cosmetic results, do not

Figure 6.—Patient with carpal tunnel syndrome with flattening of the thenar eminence indicating muscle atrophy. A swollen area is also present just proximal to the wrist joint and the flexor retinaculum.

give adequate exposure and may result in an inadequate decompression or injury to the structures. Care should be taken to avoid inadvertent injury to the motor branch of the median nerve that innervates the thenar muscles. It is wise to locate this branch and make certain that it is not selectively compressed. Preoperative evidence of thenar muscle atrophy usually indicates prolonged compression of the median nerve (Figure 6). When this condition is present, an internal neurolysis of the nerve should be performed as an adjunct to the decompression. This additional procedure may improve the results of the operation in selected cases; it has improved the recovery rate of thenar atrophy postoperatively.[34] Other possible indications for internal neurolysis are thenar muscle weakness, constant prolonged sensory loss, or failure of previous decompression. Patients should be encouraged to move the operated extremity as soon as possible to maintain elbow and shoulder motion. Slings are to be avoided, as they immobilize the entire extremity and frequently result in stiffness of the elbow or shoulder, which often require months of rehabilitation.

After the median nerve, the ulnar is probably the most commonly affected nerve; compression can occur either at the elbow or at the volar side of the wrist. At the wrist, the nerve lies within its own tunnel, the ulnar tunnel, also called Guyon's canal. The only other structure normally within the canal is the ulnar artery. The nerve can be compressed within the ulnar tunnel or after the nerve passes through the canal and divides into a sensory and a motor branch.

Figure 7.—Atrophy of the first dorsal interosseous muscle in a patient with entrapment of the ulnar nerve at the wrist. The muscle is usually large and is located at the radial side of the index metacarpal bone.

Figure 8.—Compression of the posterior tibial nerve by an anomalous muscle within the tarsal tunnel.

Therefore, symptoms and signs can be confusing, as it is possible to have primarily motor or sensory findings, depending on the entrapment site. The physical tests that should be done in these patients include the wrist flexion test and the Tinel sign. An Allen test, however, should also be done to test the patency of the ulnar artery, inasmuch as a thrombosed artery can produce the nerve compression. As the ulnar nerve usually innervates the intrinsic muscles of the hand, these muscles should be carefully examined. The muscle easiest to see and test is the first dorsal interosseous that lies on the radial side of the index metacarpal (Figure 7). It abducts and also flexes the index finger at the metacarpophalangeal joint.

The ulnar nerve can be palpated at the medial side of the elbow posterior to the medial epicondyle, and may even subluxate out of its normal location as a result of elbow motion. In addition to decompressing, this nerve should also be moved to the anterior surface of the elbow, so that the entrapment will not recur. During the procedure, the motor branches to the flexor profundus and the flexor carpi ulnaris should be identified; this frequently requires intraneural dissection so that the nerve can be adequately mobilized. A more proximal entrapment of the ulnar nerve is very rare unless an injury or an area of scar tissue is present.

Entrapment of the radial nerve, although infrequent, usually occurs about the lateral side of the elbow and often involves the deep posterior interosseous branch of the nerve. Although there is usually no wrist drop, a weakness or loss of finger extension at the metacarpophalangeal joint occurs. Entrapment in this area is often produced by some type of mass such as hypertrophied synovium of the elbow and subluxation of the radial head seen in rheumatoid arthritis, lipoma, fibroma or ganglion. Operative correction requires removing the compressive mass.

Entrapments in other areas of the upper extremity have been previously discussed and are extremely rare. Each entrapment, however, should be considered individually when evaluating the signs and symptoms that indicate entrapment of the median, ulnar or radial nerves; otherwise they will be overlooked.

Peripheral entrapments in the lower extremity also occur infrequently. The peroneal nerve can be compressed by a ganglion or a similar mass. Compression of the posterior tibial nerve at the tarsal tunnel usually results in symptoms of pain, tingling or numbness of the foot, accentuated by activities (Figure 8). Conservative treatment is frequently ineffective, and division of the flexor retinaculum (similar to decompression of the median nerve in the carpal tunnel) provides the only effective treatment of this syndrome.[35] Cutaneous sensory nerves, such as the lateral femoral cutaneous branches of the saphenous nerve, and the superficial peroneal nerve, can also be compressed at entrapment points, usually where the nerve pierces the deep fascia. Their location can be confirmed by the injection of a local anesthetic;

when symptoms are severe, they can be relieved by decompression.

Decompression of peripheral nerves can often be done without significant difficulty. The success of the operation, however, depends on establishing an absolutely accurate preoperative diagnosis, as well as carrying out a gentle but thorough procedure.

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Refer to: Meningococcus—Medical Staff Conference, University of California, San Francisco. West J Med 127:314-324, Oct 1977

Meningococcus

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and Robert C. Siegel, Associate Professor of Medicine and Orthopaedic Surgery, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *It has been our custom to ask our chief medical residents at Moffitt Hospital to discuss a topic at Medical Grand Rounds near the conclusion of their residency year. We have been privileged to have Dr. Evan Slater as chief resident during this past year. Evan will discuss the topic of the meningococcus and its control.*

DR. SLATER:† It is not a simple task to choose a topic to discuss at Grand Rounds when one is trained in general internal medicine, and has no in depth experience in any particular subspecialty area. I want to assure everyone that I am not an expert in infectious disease. However, during my two years in the Army, stationed at a basic training post, I did have the experience of sharing in the care of six patients with meningococcal disease.

I became interested in why infection with this organism seemed to affect apparently similar persons so differently, as well as what was known about its epidemiology and how its spread could be controlled.

Today, I would like to review the clinical features of the spectrum of illness caused by this organism, the factors that might influence host susceptibility and clinical expression of disease, and the present status of immunoprophylaxis and chemoprophylaxis. I will begin by presenting two very different cases of infection with Neisseria meningitides.

Case Summaries

The first patient was an 18-year-old white man, a basic trainee, who entered the acute respiratory disease ward with complaints of sore throat, cough, malaise, anorexia and fever to 104°F. He said that rigors, rash, stiff neck or neurologic symptoms had not been present, but did complain of a mild and generalized headache. On physical examination, blood pressure was 120/80 mm of mercury, pulse 105 and regular, temperature 102°F (38°C). Findings on examination of the head, eyes, ears, nose and throat were unremarkable except for an erythematous throat; there was no exudate. The neck was supple without nodes and the chest was clear to percussion and auscultation. The heart was unremarkable and examination of the abdomen showed no palpable organomegaly. On the skin and extremities no rash or petechiae and no findings suggestive of arthritis

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were noted. On neurologic examination the patient was an alert and oriented young man in whom there were no focal or abnormal findings. Laboratory examination gave the following values; leukocyte count, 12,000 per cu mm with 84 polymorphonuclear leukocytes, 4 bands, 10 lymphocytes and 2 monocytes; hematocrit reading, 39 percent; hemoglobin value, 13.4 grams per dl; platelets, 255,000 per cu mm, and the stool guaiac, negative.

The patient was well and afebrile after 48 hours. Blood cultures drawn upon admission and a throat culture grew out Neisseria meningitidis, group Y. Repeat blood cultures and lumbar puncture were negative. Treatment was begun with 20 million units of intravenously given penicillin for three days and then switched to orally given penicillin; he then returned to duty. Repeat throat cultures at discharge were negative.

The second case was that of a 19-year-old previously healthy black man, a basic trainee, who was admitted to the hospital with a five-day history of a nonproductive cough and sore throat. Several hours before admission he experienced cramps in his legs and back but said that there had been no headaches, skin rash or neurologic symptoms. On physical examination the patient was alert, oriented, and appeared healthy. Blood pressure of 115/70 mm of mercury, pulse 110 and regular, respirations 16 and temperature of 102.6°F (39°C). Examination of the head, eyes, ears, nose and throat showed only pharyngeal hyperemia. The neck was supple and the chest was clear to percussion and auscultation. The heart and abdominal examination results were unremarkable, and extremities had no rash or petechiae. On neurologic examination, the patient was alert and oriented and there were no localizing findings.

Twelve hours after admission the patient became disoriented and lethargic. Repeat examination showed nuchal rigidity, petechiae over the right leg and flank, and a generalized macular erythematous rash. Blood pressure was 70/40 mm of mercury with a pulse of 140 and regular. Peripheral leukocytes were present at 20,600 per cu mm with a leftward shift. Prothrombin time was 17 seconds and partial thromboplastin time was 58.7 seconds. The platelet count was 62,000 per cu mm. Lumbar puncture showed an opening pressure of 320 mm of water, and examination of cerebrospinal fluid showed 5,000 white cells per cu mm, 96 percent of which were polymorphonuclear leukocytes. The glucose level in the cerebrospinal fluid was 21 mg per dl and the protein value was 283 mg per dl. Gram stain of that fluid showed Gram-negative diplococci. Blood cultures and cultures of the cerebrospinal fluid subsequently grew out Neisseria meningitidis, group C. Treatment with aqueous penicillin, 2 million units given intravenously every two hours, was started. Four hours after the commencement of penicillin therapy the patient became comatose and shortly thereafter a respiratory arrest occurred for which he was intubated.

He remained hypotensive in spite of a central venous pressure of 15 cm of water. Digoxin, hydrocortisone sodium succinate (Solu-Cortef®) and dopamine were added to his regimen. After a few hours of initial improvement, the patient again became hypotensive and oliguric, and a fatal cardiac arrest occurred on the third hospital day.

Postmortem examination showed an exudative meningitis with microscopic evidence of small vessel inflammation and foci of hemorrhage in the cortex of the brainstem. There were moderate adrenal hemorrhage and extensive ecchymotic skin lesions. The heart had multiple areas of inflammation, some associated with the foci of hemorrhage.

An entirely satisfying explanation for the individual variability in host response to meningococcal infection, as illustrated by these two cases, is not available. By reviewing some of the studies of both the host and the organism, we may find a reasonable hypothesis to explain such divergence of clinical expression.

Although meningococcal disease undoubtedly existed long before, it was not separated from other causes of epidemic illness until a small outbreak was described in Geneva in 1805 by Vieusseux. The first report from the United States was in 1807 when an epidemic of "spotted fever" raged in New England. Since then, in addition to an appreciable number of sporadic cases—at present averaging about 2,000 per year in the United States—there have been several epidemics, usually associated with wars or in socioeconomically deprived areas characterized by overcrowded living conditions. Table 1 is a partial list of meningococcal epidemics that have occurred in this century.

Meningococcal disease is a disease of the young, and only 35 percent of reported cases in the United States are of an age that would be

TABLE 1.—*Major Meningococcal Epidemics—20th Century*

1904-1905—New York City—6,755 cases with 80 percent mortality
1917-1919—World War I—5,900 cases with 31 percent mortality (sixth most frequent cause of death)
1927-1931—Epidemics in Indianapolis (270 cases) and Detroit (724 cases)
1941-1943—Santiago, Chile—4,464 cases or one case per 300 inhabitants
1940-1945—World War II—14,504 cases with 3.8 percent mortality (reflecting sulfonamide therapy)
1940-present—Sub-Sahara Africa — estimated 100,000 deaths
1964-1971—United States military—pronounced increase in cases reflecting emergence of sulfa resistant organisms.
1966-1967—Netherlands—516 cases, Group B
1972-1974—Brazil—Group C, sulfa resistant
1974-1975—Finland — Group A; Northern Norway, Group B—mortality of 14 percent

TABLE 2—*Clinically Important Serogroups of the Meningococcus*

Group A—rare in the United States at present (1.5 percent)—responsible for most major epidemics; prevalent group in Sub-Sahara Africa; vaccine available; 30-40 percent sulfonamide resistant
Group B—responsible for largest number of sporadic cases in United States at present (45 percent)—small amount of poorly antigenic polysaccharide capsule; no vaccine; 5 percent sulfonamide resistant
Group C—prevalent group in military in late 1960's—30 to 35 percent of cases in the United States at present; vaccine available; approximately 70 percent sulfonamide resistant
Group Y—common in carriers—recent increase in cases in military; no vaccine; approximately 2 percent sulfonamide resistant
Groups Z, X, 29E, 135—rare but all have been reported in carriers and as cause of disease

seen by an internist. In fact, the highest incidence of cases occurs in children less than 4 years old. There is also a "meningococcal season" with 60 to 65 percent of cases occurring in the first four months of the year. There seems to be no ethnic or racial predisposition to development of overt disease that cannot be explained by environmental conditions.

The Organism

Neisseria meningitides is a fastidious, Gram-negative diplococcus, variably described as biscuit or coffee bean-shaped, that grows best on chocolate agar in the presence of 5 percent carbon dioxide. Use of Thayer Martin media, which has improved the isolation of the gonococcus from the genitourinary system, rectum and pharynx, is of benefit for the isolation of the meningococcus from sites of colonization or infection where bacterial overgrowth may be a problem. In cerebrospinal fluid and blood, the usual sources of positive cultures in clinical meningococcal disease, chocolate agar is superior to Thayer Martin media for supporting growth of the organism.

The meningococcus shares many characteristics with the gonococcus. They are morphologically very similar. The meningococcus and gonococcus are easily separated from other Neisseria by their inability to grow on plain nutrient agar at 22°C. Aside from slight difference in colony appearance, a single difference in sugar fermentation is responsible for the separation of the meningococcus from the gonococcus in the laboratory. To add to the potential for confusion, there is a surprising degree of clinical overlap with meningococcal cervicitis, conjunctivitis and urethritis, as well as several reported cases of gonococcal meningitis.

Serogroups

Meningococcal strains are divided into several serogroups on the basis of antigenic differences in capsular polysaccharides. The determination of the serogroup can be made in the case of groups A and C by a Quellung test, in which the addition of the corresponding antisera leads to capsular swelling. Serogroups are further identified by agglutination with appropriate antisera. Table 2 lists the major clinically important serogroups and their related clinical characteristics.

By absorbing the antibodies to polysaccharide antigen, bactericidal antibodies to other as yet unidentified meningococcal antigens have been found, allowing further serotyping within a serogroup.[1] This has made epidemiologic study of meningococcal carriage and disease more exact and has lent support to the concept of variable virulence of different meningococcal strains. Serotyping within serogroups has also been accomplished on the basis of differential sensitivity to bacteriocins, an antibacterial substance produced by bacteria. In the case of the meningococcus, strains to be typed are grouped according to their sensivity to bacteriocins produced by specific indicator strains.[2]

Clinical Spectrum

I should like to discuss the clinical aspects of disease caused by the meningococcus. Appropriately, I shall begin with consideration of the

carrier state since all meningococcal related problems begin with nasopharyngeal carriage of the organism. Humans represent the only recognized reservoir for the meningococcus with the portal of entry being the nasopharynx and upper respiratory tract. In the civilian population the prevalence of carriers is from 2 to 10 percent. Carriage of the organism has been documented to persist from several days to many months with an average duration of 9.6 months in one study of a normal civilian population.[3] This same study found that during a 32-month observation 18 percent of the population at some time carried a meningococcus with a prevalence rate of 5 to 10 percent. Therefore, it seems unlikely that infrequent contact with the meningococcus would be responsible for an individual person's susceptibility to infection. The meningococcus most likely spreads from person to person by airborne droplets or by inanimate objects (such as eating utensils) which are contaminated by secretions of persons harboring the organism. It is likely that the sensitivity of the organism to adverse physical conditions makes close interaction between people necessary for its spread. This is consistent with epidemiologic studies showing that only close contacts of cases of meningococcal infection are at a statistically increased risk for carriage and disease.

Whether carriage of the meningococcus causes local pharyngeal symptoms is disputed. Most studies of large numbers of carriers are from the military where in some reports up to 80 to 90 percent of trainees will become carriers during an eight-week basic training period. Because viral pharyngeal and upper respiratory infection are commonplace, clear cause and effect relating the carrier state to pharyngeal symptoms is difficult. Regardless of local symptoms, it is evident that in certain susceptible persons there follows blood stream invasion by the meningococcus.

The clinical consequence of this event is a spectrum of disease from spontaneous clearing of the bacteremia to fulminant endotoxic shock with disseminated intravascular coagulation and death. Numerous organs including most commonly the meninges may be seeded by the meningococcus, but the susceptibility of the myocardium, heart valves, synovium, peritoneum and lung add further to the variability of clinical presentation.

All factors that play a role in determining which newly acquired carrier will develop bacteremia are unknown but there are three areas where data are available. The immune status of a person seems to be the most important determinant of his or her susceptibility to meningococcal disease. Evidence for such is derived from two independent observations.

Titers of bactericidal activity are inversely correlated with the incidence of disease.[4] Newborns are protected for several months by transplacental IgG antibody but with the onset of physiologic hypogammaglobulinemia, the titer of bactericidal activity drops and the number of cases increase. How does a person acquire bactericidal activity against the meningococcus without an even higher incidence of overt clinical disease? The carrier state has been shown clearly to be an immunizing process giving rise to antibodies against several meningococcal antigens.[5] It is postulated that cross-reacting antibodies develop during the carriage of nonpathogenic meningococci as well as during immunologic reaction to other Gram-negative organisms that share antigens with the meningococcus. Thus it would not be necessary for a person to carry a pathogenic strain of the meningococcus to develop protective bactericidal antibodies. The most convincing evidence for the importance of the immune state is the result from a prospective study by Goldschneider, Gotschlich and Artenstein in 1969.[4] Table 3 shows that stored baseline sera from patients in whom systemic meningococcal disease eventually developed lack bactericidal activity against the homologous disease-producing strain of meningococcus. Only 5.6 percent of baseline sera from cases had bactericidal activity as compared with 82.2 percent of controls. Furthermore, baseline sera from cases were relatively deficient in ability to kill other disease producing meningococci although they were equal to control sera in bactericidal activity against a group Y meningococcus isolated from a carrier. Other causes of impairment of bactericidal activity, such as problems with complement, were excluded. Quantitative immunoglobulins were normal. The presence of serum bactericidal activity was correlated with presence of antimeningococcal antibodies. These patients were able to mount an antibody response as shown by serum bactericidal activity studied at an average of one month after onset of disease. The implication of these findings is that susceptible persons are deficient in antimeningococcal antibodies because they have not received significant prior exposure to meningococcal antigens.

Secretory antibodies to meningococci are found in nasal washings in a significant percentage of immune persons but their role in the prevention of clinical disease is unclear.

Dissemination of the meningococcus appears to be related to the variation of virulence of different strains. By using the serotyping techniques mentioned earlier, investigators at Ft. Dix, New Jersey, and Ft. Lewis, Washington, found that among six serotypically different group C meningococci in patients with overt disease, a single serotype was responsible for 57 of 70 cases during a six-year period of observation. Further evidence is derived from a study by Frasch and Chapman[5] from Minnesota where they looked at the frequency of serotypes of group B organisms from both carriers and patients collected over eight years from a variety of sources. They found a single serotype responsible for 30 of 55 cases, but in only 11 of 49 instances was it found in a carrier. Out of 41 isolations of their serotype 2, 73 percent were from patients with meningococcal disease, whereas out of isolations of nonserotype 2, only 31 percent were from patients with clinical disease. Although indirect, this evidence does imply that certain serotypes are more virulent and more often associated with clinical disease.

A third area of interest in explaining susceptibility to meningococcal dissemination is the role of antecedent or concomitant viral infection. Although many of the data from studies examining this question have been anecdotal, two studies have approached the problem in a systematic way. Young and colleagues studied the outbreak of nine cases of group B meningococcal infections (with three deaths) among 55 women confined to a single ward in a mental institution.[6] A concurrent outbreak of A_2 influenza affecting 50 percent of the population was also documented. There was a statistically significant increase in experience with the meningococcus (judged by culture and development of antibodies) in those patients with serologic evidence of influenza. Since the percentage of patients with overt disease was similar, the authors concluded that concomitant or antecedent influenza infection predisposed a person to acquiring the meningococcus but did not decrease local resistance to invasion.

A second study, this time in the military by Artenstein, examined the incidence of meningococcal carriage and disease in a group of trainees vaccinated with attentuated type 4 adenoviral vaccine.[7] They found that in spite of significant increase in frequency of adenoviral related upper respiratory infection in controls there was no increase either in meningococcal carrier rate or in meningococcal disease.

In summary, it seems that susceptible adults are those who have not had sufficient exposure to antigens of pathogenic meningococci, who may have antecedent or concomitant influenza infection and, finally, who are unlucky enough to have close contact with one of the few percent of people who carry a virulent strain of meningococci.

There is one other form of localized meningococcal disease that has received some recent attention in the literature. In 1919, during the influenza epidemic, there were over 100 cases of meningococcal pneumonia reported. More recently there has been a resurgency of interest in this entity, with several case reports of nonseptic

TABLE 3—*Meningococcocidal Activity of Baseline Sera* From Prospective Cases of Meningococcal Disease (From Goldschneider et al[4])*

	Bactericidal Titer 1.4 or Greater		
	Base Line Sera From Cases	*Base Line Sera From Controls*	
Meningococci	*Number Positive Total (Percent)*	*Number Positive Total (Percent)*	*Statistical Significance*
Homologous strains†	3/54 (5.6)	444/540 (82.2)	$p<0.001$‡
Other pathogenic strains			
A1 (serogroup A)	4/23 (17.4)	166/230 (72.2)	$p<0.001$§
B11 (serogroup B)	3/23 (13.0)	179/230 (77.8)	$p<0.001$§
C11 (serogroup C)	2/23 (8.7)	154/230 (67.0)	$p<0.001$§
Strain from carrier (G-2-81) (Serogroup Y)	21/23 (91.3)	221/230 (96.1)	$p>0.750$§

*Obtained from recruits in first week of basic training at Fort Dix, New Jersey, 1967-1968.[4]

†Isolated from patients whose baseline sera were tested. Baseline serum from each case of meningococcal disease was tested against his own meningococcal strain. Baseline sera from ten controls were tested against each strain (total 540 control sera).

‡Calculated using Fisher's exact test for 2×2 tables.

§Calculated by the method of X^2.

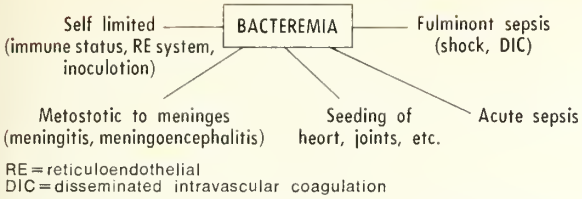

Figure 1.—Clinical concomitants of meningococcal bacteremia.

patients whose transtracheal or lung aspirate culture grew only meningococci. Therapy with penicillin was followed by prompt clinical responses in most cases. There seems to be no distinctive clinical presentation of meningococcal pneumonia although it often follows an antecedent viral respiratory illness and is usually a bronchopneumonia, radiographically. A very recent study from an Air Force recruit center reported 68 cases of meningococcal pneumonia, all caused by serogroup Y, suggesting this particular serogroup may have an unusual propensity to cause primary pneumonia.[8]

Figure 1 shows a rather artificial classification of the clinical concomitants of meningococcal bacteremia. Bacteremia may result in a self-limited illness, as was the case in the first patient presented above. Factors such as the immune state, organism virulence, activity of the reticuloendothelial system and actual volume of inoculation have been suggested as being important in containing the sepsis. Bacteremia may result in metastatic infection to the meninges with the usual symptoms associated with meningitis. Other more focal central nervous system symptoms may occur, correlating with a meningoencephalitis at autopsy. Other organs may be seeded leading to presentation as either a primary cardiac or rheumatologic problem. Cases of culture-positive pericarditis with tamponade, acute bacterial endocarditis and septic arthritis are well described. The organism may also seed the peritoneum, lung or bone with resultant local symptoms. Acute sepsis with skin rash, hemodynamic changes and positive blood cultures but without organ seeding is a relatively common presentation. Lastly, bacteremia may result in fulminant disease with shock and disseminated intravascular coagulation with all its ramifications.

This schema is artificial in that in many patients clinical categories may coexist, such as our second case with coexistent fulminant meningococcemia and meningoencephalitis.

A characteristic feature of meningococcemia which may be an early clue to the diagnosis is the skin involvement, seen in up to 65 percent of the cases. The earliest rash is a fleeting macular eruption which blanches on pressure. The lesions then may become petechial and progress to purpura and ecchymosis. The skin lesions have been correlated with survival. In one series those patients with large purpuric or ecchymotic rashes had a 44 percent mortality as opposed to a 3 percent mortality in those with petechiae or maculopapular rash only.[9]

Some interesting experimental observations have been made in the search for reasons why skin involvement is so common in meningococcemia as compared with other causes of sepsis. Endotoxin isolated from the meningococcus was compared with endotoxin from several other Gram-negative bacteria in its ability to produce skin necrosis in rabbits. The endotoxin isolated from the meningococci, despite only minor chemical differences from control endotoxin and with no evidence of increased localization in the skin, was five to ten times more potent in producing skin lesions in this experimental model.[10]

Another form of meningococcal bacteremia should be mentioned for completeness although in the antibiotic era the syndrome of chronic meningococcemia is rare. This illness was originally described in 1902 and is characterized by intermittent fever, arthralgias, malaise, anorexia, weight loss, splenomegaly and skin rash varying from petechiae to erythema nodosum-type lesions.[11] If patients with this syndrome are not treated, eventually their meninges or cardiac structures may be seeded and clinical features more like those of acute meningococcal disease may develop. Therapy with penicillin at any time during the course of the illness is usually curative.

On adult medical services in American hospitals, the culture and Gram stain of appropriate clinical material is the mainstay of diagnosis. Cerebrospinal fluid should always be Gram stained even if no cells are present because bacteria without cells is not a rare observation and has been associated with a poor prognosis. Gram stain of the buffy coat may also be revealing in meningococcemia. Two reports from the 1940's claim a higher yield of positive culture and Gram stain from blood obtained from scraping purpuric skin lesions as compared with routine blood cultures.[12,13]

The detection of meningococcal antigen in blood and cerebrospinal fluid (CSF) as measured

TABLE 4—*Comparison of Immunoelectrophoresis and Routine Bacteriologic Study of Cerebrospinal Fluid in the Diagnosis of 191 Patients with Meningococcal Meningitis (From Whittle et al[14])*

Method	*Number*	*Percent*
Immunoelectrophoresis positive ...	129	67.5
Gram stain or culture positive	125	65.4
Either positive	162	84.8
Both negative	29	15.2

by countercurrent immunoelectrophoresis (CIE) has been found to increase the frequency of definitive diagnosis as well as to be of some prognostic significance in terms of survival and the development of a postinfection polyserositis syndrome.[14]

Table 4 compares the immunoelectrophoresis and routine bacteriologic studies of CSF, and documents the value of immunoelectrophoresis for establishing the diagnosis. Of the patients 65 percent are either culture positive or CIE positive, but by combining the two techniques 85 percent will have positive objective evidence of meningococcal disease. The 15 percent false negatives were diagnosed on the basis of clinical presentation and acute and convalescent antibody titers. In medically deprived areas where cultures are not easily done—for instance in Nigeria—countercurrent immunoelectrophoresis can and has replaced routine culture. CIE also has been shown to be of particular value for confirming the diagnosis in patients partially treated with antibiotics. Several studies have confirmed that the higher the titer of meningococcal antigen in the CSF or blood, the greater are the mortality rates and the complications of the clinical illness.

There is a curious recovery phase serositis that occurs in 10 to 15 percent of patients with meningococcemia. After initial improvement with antibiotic therapy, the patients become febrile again between the 4th and 10th days and present a variable combination of arthralgias, arthritis, pericarditis, pleuritis, episcleritis and cutaneous vasculitis. All repeat cultures are usually negative. The symptoms generally resolve without intervention although occasionally steroids have been used in patients with severe pericarditis or arthritis. The pathogenesis of this postinfectious syndrome is unclear. Drug reaction seems unlikely since the syndrome was described before the use of antibiotics, and discontinuing or changing drugs seems to have no effect on the natural course of the disease. Although L forms of meningococci can be produced in the laboratory by exposure to antibiotics, there is no evidence that they are associated with clinical illness. Whittle and Greenwood have made several observations in Nigeria that imply that immune complexes are involved in the pathogenesis of this syndrome.[15] They found a statistically significant correlation between presence of meningococcal antigen in serum and the subsequent development of the polyserositis syndrome. In some patients they noted a depression of the third component of complement (C_3) and total complement, and by using Clq binding techniques they have been able to measure circulating immune complexes in a few patients. Further, by immunofluorescent techniques they were able to detect deposits of meningococcal antigen, immunoglobulin and C_3 in the leukocytes from the synovial fluid of two patients and from the skin biopsy specimens in one. Regardless of the pathogenesis, it is important clinically to recognize this syndrome as it is usually self-limited, does not require a change in dosage or type of antibiotic, and only rarely will require anti-inflammatory agents.

As far as the therapy of meningococcemia is concerned, the importance of early recognition and institution of therapy cannot be overemphasized.[16] If one suspects meningococcal disease and cannot definitely rule it out, the patient should be treated with antibiotics pending cultures. The drug of choice is intravenously given penicillin. No strains resistant to this drug have been identified. The dose is 20 million units per day in divided doses every two hours. In patients with known anaphylaxis to penicillin, intravenously given chloramphenicol, 4 grams per day, is second choice. Cephalosporin should not be used because inadequate CSF levels are attained, and meningitis has actually been reported to develop in patients receiving cephalosporin for other indications.[17]

There are many important complications and sequelae of meningococcal disease (Table 5). Clinically important disseminated intravascular coagulation occurs in 10 to 20 percent of reported cases. Its pathogenesis is most likely related to hypotensive and endotoxin induced endothelial damage with direct and indirect activation of the clotting mechanism. The efficacy of heparin in this situation is disputed. It has been given both prophylactically and after clinical problems with bleeding have occurred. It can be stated that heparin can be given safely without undue risk of CNS or subarachnoid bleeding and that it is effective in improving clotting. Improvement in

TABLE 5—*Complications and Sequelae of Meningococcal Disease*

- Disseminated intravascular coagulation—10 to 20 percent—gangrene, renal failure—? role of heparin
- Central nervous system disease—cranial nerve palsies, seizure, normal pressure hydrocephalus
- Myocarditis—80 percent at autopsy—arrhythmias, congestive heart failure—? therapeutic indications
- Pericarditis—tamponade with positive culture
- Adrenal hemorrhage—20 percent at autopsy—unlikely to be functionally significant
- Acute respiratory distress syndrome—uncommon

mortality, however, has not been satisfactorily shown. As in most clinical situations with disseminated intravascular coagulation, treatment of the underlying disorder is of primary importance.

CNS sequelae are now relatively uncommon, occurring in less than 5 percent of patients. Cranial nerve palsies, especially of the 8th nerve, seizure disorders and normal pressure hydrocephalus are the most frequently encountered neurologic complications.

Myocarditis has been found at autopsy in up to 80 percent of patients in some series.[18] Atrial and ventricular arrhythmias have been reported. Pump failure secondary to myocarditis may contribute to hypotension and may possibly be improved by use of ionotropic agents. In the approach to hypotensive patients with meningococcal sepsis one must be aware that there have been several reports of culture positive cardiac tamponade.[19]

Adrenal hemorrhage, or the Waterhouse-Friderichsen syndrome, has received excessive emphasis relative to its clinical importance. Most studies measuring serum cortisol levels in patients with adrenal hemorrhage have found them to be high, making it unlikely that acute adrenal failure contributes to the hypotension present in many of these patients. Furthermore, there has been no reported case of adrenal insufficiency among the survivors of fulminant meningococcemia.

Acute respiratory distress syndrome with noncardiac pulmonary edema occurs uncommonly and is indistinguishable from the syndrome found in other hypotensive, bacteremic shock situations.

The problem of prophylaxis in meningococcal disease is complex.[20] Some investigators have suggested that diligent surveillance for early disease among the close contacts of patients is adequate. Unfortunately, as we have discussed, meningococcal disease can follow an extraordinarily rapid and fulminant course, making this approach to secondary cases hazardous. Before discussing other approaches to prophylaxis we have to know the risks for contacts of patients with meningococcal disease. Table 6 shows the secondary attack rate in a number of epidemic situations. The number of secondary cases in the endemic situation is much less—averaging 3/1,000 household members but is still 1,000 times the overall endemic rate. Although it has been estimated that a maximum of only 45 cases per year in the United States can be prevented by appropriate therapy of close contacts, prophylaxis is certainly indicated.

It has been fairly well established by epidemiologic studies that only close contacts of patients such as household members and sexual partners should receive prophylaxis. The secondary attack rate for casual contacts such as school or job acquaintances is very close to the prevalent endemic rate. Until recently the only approach to prophylaxis reflected the concept that elimination of the organism from nasopharyngeal carriage would prevent disease. The almost

TABLE 6—*Meningococcal Disease Secondary Attack Rates in Five Urban Serogroup A Epidemics (From Meningococcal Disease Surveillance Group[20])*

	Source				
	Lee	*Gordon*	*French*	*Pickett*	*Pizzi*
	Indianapolis, 1929-1930	*Detroit, 1928-1931*	*Milwaukee, 1927-1929*	*Saginaw, Michigan, 1929*	*Chile 1941-1942*
Households with one or more cases	109	1,581	363	251	....
Households with two or more cases	11	65	14	11	....
Number in household	403*	5,850*	1,530	929*	9,668
Secondary cases†	18	78	17	13	247
Rate of secondary cases					
Households, percent	10.1%	4.1%	3.8%	4.4%	....
Household members per 1,000	45	13	11	14	25

*Assumes household size of 3.7, excluding case.
†Co-primary cases included (exception, Milwaukee data).

TABLE 7.—*The Effect of Minocycline and Rifampin on Meningococcal Carriers (From Guttler et al[22])*

	Antibiotic			
	Minocycline		Rifampin	
	Number	Percent	Number	Percent
Initial eradication	36/38	95	43/51*	84
Five-week eradication	28/38	74	38/51	75
Relapse	8/38	21	5/51	10
New carriers	15/105	14	11/86	13
Failures	2/38	5	8/51	16
Carriers of resistant strains	0	0	12/62†	27

NOTE: Initial eradication = positive initially, negative during therapy; five-week eradication = positive initially, negative during and five weeks after therapy; relapse = positive initially, negative during therapy, positive after therapy; new carriers = negative initially, positive after therapy; failures = positive during and after therapy.

*Denominator includes three recruits with negative cultures initially but positive cultures while on therapy and subsequently.

†Denominator includes all carriers before and after therapy.

universal susceptibility of meningococci to sulfonamides, the rapid and persistent elimination of the organism from the nasopharynx after a short course of sulfa, and the rarity of side effects associated with administration of the drug, made sulfonamide an ideal chemoprophylactic agent. Its efficacy was proven in the 1940's by a controlled trial in the military.[21] In a population of 18,000 untreated soldiers 44 cases of meningococcal disease developed as compared with only two cases of meningococcal disease appearing among 15,000 men treated prophylactically with 2 grams of sulfadiazine for two days. Through the 1940's and 1950's the sulfonamides were widely and successfully used as prophylactic agents both in the civilian and military population. In 1963 the emergence of sulfonamide resistant meningococci was documented. Sulfonamides were shown to no longer be effective chemoprophylactic agents except when it was known that the disease causing meningococcus was sulfa sensitive. Since the highest incidence of secondary cases occur within the first week following exposure, it was not rational to withhold chemoprophylaxis to await sensitivity results. Penicillin, ampicillin, erythromycin and other antibiotics were tried as prophylactic agents but were ineffective in eliminating the carrier state for any length of time.

At present there are two drugs which have been shown to be effective in elimination of the carrier state although neither has been tested for efficacy in prevention of secondary cases. The first is rifampin in a dosage of 600 mg every 12 hours for four doses, and the second is minocycline, a semisynthetic tetracycline, given as 100 mg every 12 hours for three days. Table 7 compares the efficacies of rifampin and minocycline in eliminating the carrier state for several weeks.[22] It also shows that a significant number of rifampin resistant organisms were cultured at follow-up. Therefore, rifampin would be reasonably effective in the sporadic endemic situation, but it should be expected to be of limited value in an epidemic. Although minocycline resistance is not a problem, the incidence of side effects is.[23] A high percentage of patients had side effects, particularly vestibular dysfunction, with the use of minocycline. Although several studies have indicated a much lower percentage of side effects, at present the Center for Disease Control recommends the use of rifampin as the chemoprophylactic agent of choice for disease caused by sulfonamide-resistant meningococci or when the sensitivities of the meningococcus are not known.

The second and most recent approach to prophylaxis for meningococcal disease has been vaccination with purified polysaccharide antigen. Some evidence for the importance of the immune status of the person in preventing disease with the meningococcus has already been presented. The idea of a vaccine is not new. In the early 1920's heat killed meningococci were actually given as a vaccine in an epidemic situation. If the patient survived the occasional systemic reaction which resembled endotoxic shock, he or she seemed to be protected from developing meningococcal disease.

Malcolm Artenstein and his colleagues at Walter Reed Army Medical Center were able to purify high molecular weight group A and C polysaccharides which although not immunogenic in laboratory animals, were highly active in inducing antibody responses in humans.[24] A single injection of 50 μg produced an antibody response in almost 100 percent of subjects tested, and mild local erythema was the only side effect. Large scale trials were then conducted in the military where group C meningococcal disease was a significant clinical problem. Table 8 shows the results of the controlled field trial of group C vaccine. As can be seen, the vaccine is serogroup specific, protecting only for group C disease.[25] The incidence of the carrier state is also decreased by the vaccine. Follow-up studies of vaccinated persons have shown that antibody levels persist for at least five years in most.

Group A vaccine has been tested in Egyptian school children and in Army recruits in Finland

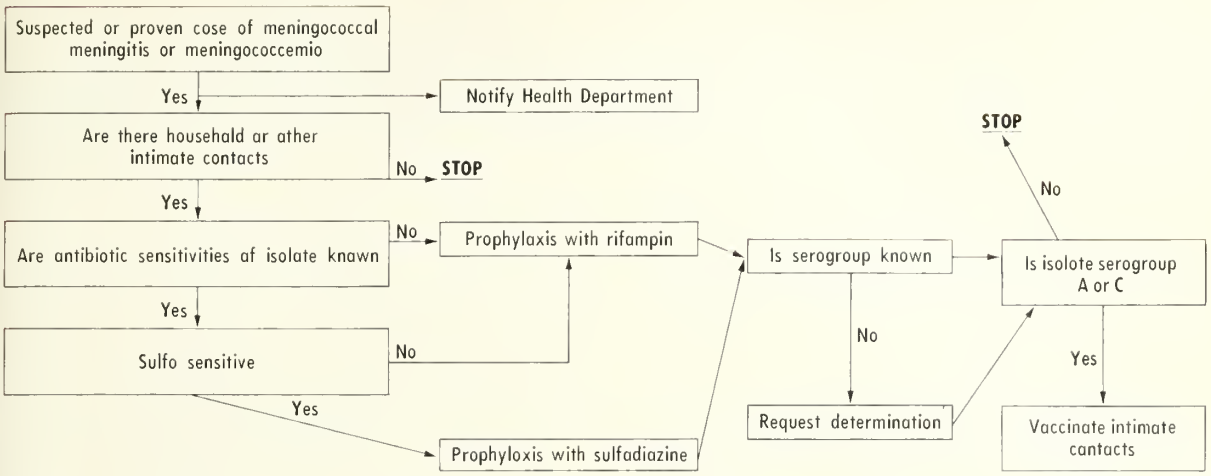

Figure 2.—Meningococcal prophylaxis (Adapted from Jacobson JA, Fraser DW: A simplified approach to meningococcal disease prophylaxis. JAMA 236:1053-1054, Aug 30, 1976).

TABLE 8—*Meningococcal Vaccines—Field Trials of Group C Meningococcal Polysaccharide Vaccines (From Artenstein et al*[25])

	Vaccine Group			*Control Group*		
		Number of cases and serogroup			*Number of cases and serogroup*	
Year	*Number of Men*	*B*	*C*	*Number of Men*	*B*	*C*
1969	13,763	4	1	54,309	3	38
1969-1970 .	14,482	0	1	60,172	0	35
TOTALS .	28,245	4	2	114,481	3	73

and decreased the incidence of disease caused by Group A meningococci. Again the vaccine is serogroup specific and offers no protection from disease caused by other serogroups.

Group B polysaccharide vaccines have been prepared and tested in several hundred volunteers, but very few subjects have shown antibody response.[26] The reasons for lack of immunogenicity are unclear, but alternative approaches such as purifying group B cell wall protein antigens and study of possible cross reaction with antigens from other Gram-negative bacteria are being pursued.

Figure 2 presents a useful algorithm for the approach to chemoprophylaxis and immunoprophylaxis of a known case of meningococcal disease. Always remember to notify the health department. If the organism is known to be sulfa-sensitive, sulfadiazine is appropriate. If the disease producing meningococcus is group A or C, vaccine should be given concomitantly with chemoprophylaxis. Administration of vaccine is necessary since the early chemoprophylaxis may blunt the immune response of a person and consequently maintain his or her susceptibility to clinical disease. Because the carrier state is long and there are a significant number of failures with chemoprophylaxis, his or her chance of close contact with a carrier still exists. Assuring an antibody response with serogroup specific vaccine should be protective.

In closing, I should like to list what I consider to be the current major problems in control of meningococcal disease.

- *Lack of an ideal chemoprophylactic agent.* If toxicity from minocycline turns out to be minimal, this potentially is a very effective drug.
- *Lack of a vaccine for group B organisms.* As mentioned, work is underway to isolate from cell walls protein antigens with sufficient immunogenicity. If successful, routine vaccination of children with a polyvalent meningococcal vaccine is a possibility.
- *Relative ineffectiveness of vaccines in children less than two years old.* This is probably because of poor antibody response due to an immature immune system. This is perhaps the greatest problem since vaccines will not eliminate carriers of virulent strains and therefore not eliminate the exposure of these susceptible children to the risk of clinical disease. Perhaps modification of the polysaccharide antigens or isolation of a different antigen will improve the immunogenicity for this age group.
- *Delay in diagnosis.* We still must rely on clinical assessment and judgment to make an early diagnosis of meningococcal disease. One

cannot afford to await culture results, and countercurrent immunoelectrophoresis, although completed in a few minutes, is not widely available. A 15 to 30 percent mortality rate in the civilian population is too high and most likely results from the delay in therapy.

By keeping meningococcal disease in mind when confronted with a febrile patient in a toxic condition, particularly when a skin rash is noted, and instituting early therapy, you can increase the patient's chances for survival.

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Early Diagnostic Esophagoscopy in the Management of Corrosive Burns of the Esophagus

AS EARLY AS WE CAN—it may be 10, 12, 14 or even 24 hours after injury—we do an esophagoscopic study in all cases of possible corrosive burns of the esophagus. It's diagnostic esophagoscopy, because all we want to find out is if the esophagus is burned or if it's not burned. If the esophagus is not burned, a patient will be in hospital for a very short time for the treatment of the burns of the lips and buccal mucosa. If the esophagus is burned, we will continue therapy with antibiotics and steroids. Barium swallows do not help us because there could be severe damage, and the scarring and stricture formation takes usually weeks to occur. So, the mistake has been made to get a barium swallow at say two weeks after injury. The results may look pretty good, yet these patients have difficulty eating. In some of them there may even be aspiration of food and we wonder why they keep having these problems. So, I think diagnostic esophagoscopy is vital to see which patient you have to treat.

—GILBERT S. CAMPBELL, MD, *Little Rock*

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Important Advances in Clinical Medicine

Epitomes of Progress — Chest Diseases

The Scientific Board of the California Medical Association presents the following inventory of items of progress in chest diseases. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in chest diseases which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Chest Diseases of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Newer Diagnostic Tests for Sarcoidosis

SARCOIDOSIS IS AN important disease entity found in all races and ethnic groups in the United States, but especially in blacks. This disease enters into the differential diagnosis of pulmonary hilar adenopathy, lung infiltrates or nodules and other systemic granulomatous problems. A diagnosis is supported primarily by biopsy of lymph nodes or lung tissue showing noncaseating granulomata. Clinically, the disease frequently presents as bilateral hilar adenopathy on an x-ray study of the chest, with evidence of multiple organ involvement.

The Kveim test, when done with an acceptable batch of Kveim reagent (usually an extract of sarcoid spleen), is positive in approximately 80 percent of patients with active sarcoidosis, but the reagent may produce reactions in appreciable numbers of patients with certain other diseases including Crohn disease, ulcerative colitis, celiac disease and tuberculous lymphadenitis. The intradermal Kveim test usually requires biopsy of a papule that develops in the skin after one to four weeks for confirmation of positivity. More recently, *in vitro* Kveim tests have been investigated in which inhibition of leukocyte migration or enhancements of lymphocyte blast formation by a Kveim test suspension is evaluated. Unfortunately, the Kveim antigen test material is not generally available and has not been approved by the Food and Drug Administration for commercial distribution.

A simple blood test recently has been reported that shows promise of being useful for confirming a diagnosis of *active* sarcoidosis. The test involves the measurement of serum angiotensin-converting-enzyme (ACE). Serum ACE levels are elevated two- to three-fold in patients with active sarcoidosis, possibly because of synthesis and release of the enzyme by the epithelioid cells making up the sarcoid granulomata. The elevated levels return to normal when the disease becomes inactive or resolved or when therapeutic doses of corticosteroids are administered. Therefore, measurements of serum ACE may be useful both for confirming the diagnosis of active sarcoidosis and for evaluating the response to therapy.

JACK LIEBERMAN, MD

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Early Detection of Chronic Obstructive Respiratory Disease

CHRONIC OBSTRUCTIVE RESPIRATORY DISEASE is one of the major and most rapidly increasing causes of disability in the United States. By the time dyspnea or reduction in spirographic forced expired volume in one second (FEV_1) develops, the disease has reached an irreversible stage. Diagnosis in the early stages is essential if medical management is to succeed in preventing progressive involvement and associated disability.

Over the past few years, a number of tests have been described which are capable of detecting chronic obstructive respiratory disease at a time when results of less sensitive tests, such as the FEV_1 are normal and the pathological condition is largely confined to the small airways (less than 2 to 3 mm in diameter). These tests include (1) frequency dependence of compliance, (2) forced expiratory flow rates calculated from the middle or terminal portion of the conventional spirogram or flow-volume curve, (3) closing volume and closing capacity (the volume at which airways in dependent lung zones begin to close) and (4) volume of isoflow calculated from maximal expiratory flow-volume curves determined with the patient breathing air and a mixture of 80 percent helium and 20 percent oxygen. Although "frequency dependence of compliance" may be the most sensitive of these tests, it is too invasive and complex for routine use. Of the other tests, the spirographic maximum midexpiratory flow rate is the simplest and the best standardized.

Recently, in more than 200 subjects, radioxenon and radioaerosol inhalation lung imaging was compared with multiple pulmonary function tests and other diagnostic procedures to determine their relative sensitivity in detecting evidence of early obstructive airway disease. Subjects were classified by the presence or absence of chronic obstructive respiratory disease by two chest physicians on the basis of all available data except the radionuclide studies. The radioaerosol procedure showed the greatest sensitivity (84 percent) in the detection of the disease but its specificity was only fair (62 percent) in comparison with flow rates at mid- and low-lung volumes which showed both good sensitivity (74 percent) and specificity (84 percent).

At present it is not possible to predict which person with isolated abnormalities on the newer screening tests for small airways dysfunction will progress to an irreversible and disabling stage of chronic obstructive respiratory disease. Longitudinal epidemiological studies of cohorts carefully defined from the clinical, environmental and physiological standpoint might answer this question. Indices of early obstructive airway disease in cigarette smokers have been found to be reversible following cessation of smoking; this observation may be of value in attempting to persuade some smokers to stop smoking.

DONALD P. TASHKIN, MD

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Transbronchial Lung Biopsy Using a Flexible Fiberoptic Bronchoscope

THE ABILITY to obtain lung tissue without the risks and trauma of thoractomy has been enhanced by the technique of transbronchial biopsy through a flexible fiberoptic bronchoscope. This procedure was originally described using a rigid bronchoscope but now has been adapted to flexible bronchoscopes.

The technique is especially useful in obtaining lung tissue in such disorders as sarcoidosis, interstitial pneumonitis, alveolar cell carcinoma, lymphangitic spread of carcinoma and pulmonary alveolar proteinosis. Proper patient preparation is helpful for optimal collection of specimens. Good suppression of the cough with lidocaine and selection of an involved segment for biopsy, as determined by x-ray studies, are important. The tip of the bronchoscope is passed visually as far as possible. Then biopsy forceps, with jaws closed, are passed peripherally to the pleura under direct fluoroscopic control. They then are withdrawn 2 to 3 cm, opened and advanced until resistance is met. If no unusual chest wall sensations are felt by the patient, he is asked to slowly exhale. At the end of the exhalation, the jaws of the forceps are closed and the forceps removed. Usually a small piece of lung parenchyma and the neighboring bronchus are obtained. Since the specimens are small (1 to 2 mm in diameter), it is best to take

several specimens to insure enough tissue for adequate examination. Fluoroscopy should be used when one attempts to take a biopsy specimen of a well-localized lesion seen on an x-ray film of the chest.

Pneumothorax does occur (in 10 percent of cases, or less), occasionally requiring chest tube insertion. Although significant hemoptysis is rare, bleeding severe enough to require open thoracotomy to resect or ligate the bleeding site has been reported and some fatalities have occurred. Careful attention to technique will limit these problems. Biopsies done in the right middle lobe and lingula have an increased risk of pneumothorax. The procedure is contraindicated in patients with pulmonary hypertension or bleeding disorders. The inability of a patient to cooperate is a distinct disadvantage, but only constitutes a relative contraindication.

RICHARD L. SHELDON, MD

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Corticosteroid Aerosols in the Treatment of Asthma

IN PATIENTS with sputum or blood eosinophilia and recurrent attacks of bronchospasm, the use of corticosteroids may be very helpful. Unfortunately, the use of orally given steroids such as prednisone, when taken for other than a short course, may lead to significant systemic side effects. Such problems as a "moon face," prominent bruising, osteoporosis, and adrenal gland suppression are well recognized complications of corticosteroid therapy.

The use of aerosolized steroids in treating asthma is not new. Dexamethasone (Decadron®) has been used as an inhalant for many years. However, the use of dexamethasone as an aerosol also may result in significant systemic side effects.

The aerosol administration of several newer corticosteroid preparations (beclomethasone dipropionate, triamcinolone acetonide and betamethasone valerate) has resulted in the benefits of steroid therapy without adverse systemic effects. In the small doses used, there is no development of significant systemic levels of corticosteroid, and adrenal function is not impaired.

The use of these new steroid aerosols has allowed patients who were dependent on large doses of oral steroids to reduce their dose to a reasonable daily level, for example, less than 10 mg of prednisone per day, and in some cases to an alternate-day regimen, thereby minimizing systemic side effects. Many patients are able to avoid systemic (orally taken) steroids completely by inhaling one of these new preparations.

The only significant adverse effect of these new steroid aerosols has been the occasional development (in approximately 5 percent of patients) of a Candida infection of the oropharynx, which responds to a reduction in dosage of the inhaled steroid along with nystatin (Mycostatin®) mouth rinse or amphotericin B lozenges. Some patients have complained of hoarseness, which improves rapidly after the steroid therapy is stopped. This hoarseness usually can be prevented by rinsing the mouth with water after each use.

In patients who have been receiving steroids for long periods, allergic rhinitis and eczema may recur and adrenal insufficiency may develop as the oral administration of steroids is discontinued. During an exacerbation of bronchospasm, such as with infection or heavy exposure to allergens, a short intensive course of systemic corticosteroids sometimes may be necessary.

Beclomethasone dipropionate (Vanceril®) is now available in cartridge-inhaler form in the United States, and is a significant addition to the therapeutic armamentarium of physicians treating patients with reversible airway obstruction.

JOHN E. HODGKIN, MD

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Cystic Fibrosis

CYSTIC FIBROSIS has been considered primarily a pediatric problem, although approximately 25 percent of patients now survive into their second decade of life. In addition, in some patients overt symptoms of the disease do not appear until young

adulthood. Consequently, physicians who primarily treat adults should be aware of this diagnosis in their evaluation of young adults with chronic pulmonary or intestinal problems.

Cystic fibrosis is inherited through an autosomal recessive gene for which analysis of sweat sodium or chloride, or both, is the key diagnostic test. A sweat chloride value (obtained by pilocarpine iontophoresis) over 60 mEq per liter usually is diagnostic of cystic fibrosis. Nasal polyposis, chronic bronchitis, bronchiectasis, evidence of pancreatic insufficiency or a family history of cystic fibrosis in a sibling are all indications for carrying out a sweat test. Pancreatic and pulmonary manifestations need not both be present in a patient to warrant a workup for cystic fibrosis because many patients are seen with either one or the other of these major manifestations.

The detection of heterozygous carriers of the cystic fibrosis gene still remains an important research problem, since genetic counseling depends on the availability of such a test. A factor that causes ciliary dyskinesia with rabbit tracheal cultures or oyster gills can be detected in homozygous and heterozygous blood, but this has not been entirely reliable for detecting the carriers. Other procedures are being investigated; one method that shows promise detects the carrier state by showing an abnormal response of protein, B-glucuronidase or ribonucleic acid (RNA) methylation in cultured lymphocytes to a stimulus by phytohemagglutinin. Cystic fibrosis is a genetic model that may be the key for understanding the pathogenesis of various chronic lung diseases, including chronic bronchitis and bronchiectasis.

JACK LIEBERMAN, MD

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Smoke Inhalation and Respiratory Failure in Burn Injury

RESPIRATORY FAILURE is the most common cause of death following burn injury. Many factors contribute to this problem, one of which is smoke inhalation. The diagnosis of smoke inhalation is made on the basis of soot-laden sputum production which often persists for several days after the injury. Carboxyhemoglobin levels over 15 percent indicate significant smoke inhalation, although carboxyhemoglobin may have largely disappeared by the time the first measurement is made. The major effects of smoke inhalation are seen on respiratory epithelium of the conducting airways. Stridor and laryngeal edema, bronchorrhea, persistent cough and all the findings of small airway obstruction from mucosal edema may occur. This damage is not inflicted by heat or carbon particles, but rather by toxic volatile gases liberated during incomplete combustion. For this reason smoke inhalation damage is rare following accidents with gasoline, kerosene, alcohol or other flammable liquids, but is commonly associated with the burning of upholstery, paint, wood and similar substances.

Respiratory effects of smoke inhalation occurring without surface burns are mild. Major smoke inhalation often is associated with brain damage and severe metabolic acidosis resulting from impaired oxygen delivery caused by the presence of carboxyhemoglobin. If the patient survives the injury without brain damage, respiratory complications are minimal. Smoke inhalation should be treated with 100 percent oxygen breathing until carboxyhemoglobin is less than 10 percent, metabolic acidosis has cleared or brain function is normal. Hoarseness or stridor usually will improve with administration of 4 mg of dexamethosone, repeated if necessary. Humidification of inhaled air is continued as long as sputum production is heavy. Bronchodilators are indicated if bronchospasm occurs. The patient may cough up soot-laden sputum and shreds of bronchial mucosa for several days. Inpatient care should be continued until the sputum is clear. Endotracheal intubation or tracheostomy rarely is necessary. Prompt fiberoptic bronchoscopy is advised to diagnose the degree of airway inflammation. Bronchoscopy is indicated also if there are signs of major airway obstruction with mucous plugs, but this rarely is necessary.

Pulmonary capillary leakage, alveolar atelectasis, interstitial edema and finally bacterial pneumonitis is a common sequence of events in patients with burns involving more than 60 percent of the body surface area. Smaller burns usually are not associated with pulmonary complications unless there is concomitant smoke inhalation. The com-

bination of smoke inhalation and surface burns greatly increases the risk of respiratory failure. In a recent series the mortality for respiratory failure caused by a combination of surface burn and smoke inhalation was 86 percent. Smoke inhalation combined with burn injury requires more vigorous management. Third degree burns of the face or neck, burns extending into the pharynx, laryngeal edema under direct examination, and hoarseness are all indications for intubation. Mechanical ventilation with positive end expiratory pressure is used to support alveolar inflation during the resuscitation period. To avoid pulmonary interstitial edema, fluid resuscitation should be carefully controlled to give the least amount of fluid which will sustain adequate peripheral perfusion. We favor the use of all colloid resuscitation fluid to maintain a high serum oncotic pressure during resuscitation. The use of a pulmonary artery catheter is a helpful guide to resuscitation in these critically injured patients. After airway edema subsides the endotracheal tube usually can be removed. If pulmonary failure later develops requiring intubation, a tracheostomy should follow. Mucous plugs are common and frequent tracheal suctioning and bronchoscopy are helpful adjuncts to ventilation. Frequent sputum cultures and treatment of pneumonitis with specific antibiotics should be done.

ROBERT H. BARTLETT, MD

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Intermittent Mandatory Ventilation

THE TECHNIQUE of intermittent mandatory ventilation (IMV) was first described in connection with the mechanical ventilatory support of infants suffering from the neonatal respiratory distress syndrome. The authors stated that the method allowed more comfortable spontaneous breathing efforts by these infants, improved gas exchange and shortened the time necessary for mechanical support.

Soon thereafter, Downs and associates described the use of IMV as a preferable method for weaning adult patients from continuous mechanical ventilatory support. Based on an uncontrolled study in patients with a variety of disorders, it was claimed that IMV when compared with conventional methods reduced ventilation time and oxygen consumption, and minimized discoordination of respiratory muscle activity during the weaning process.

Subsequently, IMV as a weaning technique virtually has exploded in popularity and in some areas has become the standard weaning method for all patients receiving mechanical ventilation.

Basically the technique involves modification of any mechanical ventilator (available from the manufacturers of most ventilators) so that the patient can spontaneously breathe a preset gas mixture as he desires; however, a mechanical ventilation also can be delivered at predetermined intervals.

In our experience as well as that of others, if a patient does not meet the well recognized weaning criteria and is therefore difficult to wean using the conventional methods, then IMV is no more effective. It can be used as a suitable alternative in patients who do not breathe synchronously with a ventilator when sedating the patient might be undesirable. With IMV, almost no sedation is required; and synchronized breathing, although desirable, is not necessary. It is probably most useful in a patient who has become psychologically dependent on mechanical support. When IMV is instituted, it is customarily begun, in an adult, at a rate half the patient's spontaneous rate. It is then reduced appropriately, based on clinical and arterial blood gas responses, until a mandatory rate of one breath per minute is achieved; then it is discontinued. In our experience, in most clinical situations there has been no advantage to continuing the reduction in mandatory rate below six breaths per minute.

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New Diagnostic Techniques for Thrombophlebitis

FORMERLY CALLED "thrombophlebitis" or "phlebothrombosis," deep venous thrombosis (DVT) of the lower extremities has posed a diagnostic problem to physicians for many years. Yet the prompt and accurate diagnosis of DVT is of major importance because more than 95 percent of clinically significant pulmonary emboli arise from thrombosis in these veins. Multiple studies now have shown that the clinical diagnosis of DVT is frequently erroneous. Approximately 50 percent of DVT episodes will escape the most careful clinical evaluation because local heat, redness, pain and edema are absent or equivocal. Furthermore, these same findings are often present in the legs of patients with nonthrombotic disorders. Thus both false negative and false positive diagnoses are quite common when the physician is restricted to clinical means for detection.

Three noninvasive techniques now are available to assist the physician in diagnosis: impedance phlebography (IPG), the Doppler ultrasound technique and leg scanning following the intravenous injection of radiolabeled fibrinogen (RLF). In addition, contrast venography is available as the standard and the final arbiter. Each of these approaches has advantages and limitations.

Impedance phlebography is a rapid, simple technique. It relies upon measurement changes in calf resistance (impedance). Inflation of a blood pressure cuff on the thigh leads to retention of blood in the calf and a fall in impedance because blood is a good conductor. Release of the cuff should be followed by rapid outflow of blood and an increase in calf impedance. Significant venous obstruction is signaled by a failure of calf resistance to return rapidly to baseline values after cuff release. The Doppler technique is quite similar in concept, but it relies upon frequency shifts in the ultrasound signal reflected from blood flowing through the femoral vein. Both techniques can be done at the bedside. False positives with both are rare. Because both tests require significant obstruction to outflow of blood from the legs, false negatives can occur with small thrombi or with old thrombi which have been bypassed by collaterals.

The radiolabeled fibrinogen test requires only that the venous thrombus is active; that is, capable of incorporating circulating RLF. This requirement is automatically met when a thrombus forms after RLF is injected. This is the circumstance which exists when RLF is used prospectively to detect the onset of DVT in certain high risk (for example, postsurgical) patients. However, in patients presenting with clinically suspected DVT, the thrombus may or may not be "active." Thrombi more than a week old (by history) are not likely to incorporate RLF. In patients receiving heparin for more than six hours (in adequate dose) results on RLF tests also will be negative.

The IPG and Doppler techniques are most sensitive to thrombi occluding the thigh and pelvic veins. RLF is most sensitive to thrombi in calf and low thigh; in the upper thigh the test is difficult to interpret because of the high radioactivity in the pelvic blood pool. Therefore, when combined, these noninvasive techniques offer a highly useful method for detecting the presence, probable location and course of DVT—and for ruling out the diagnosis.

The correlation between contrast venography and the results of impedance-Doppler-RLF studies has been of high degree in most studies. Contrast venography is, of course, the only diagnostic technique by which venous thrombi can be visualized. However, the technique is invasive, requires special skill in performance and interpretation, and can induce and extend venous thrombosis. It is not an attractive technique for repetitive application.

With the methods now available, physicians are in a position to accurately determine the presence or absence of DVT with a high degree of accuracy, despite the variable clinical expressions of the disorder.

Selection of the most appropriate laboratory study will depend upon availability and the particular clinical context of the patient. The physician's ability to make such selection optimally requires that he gain familiarity with the advantages and limitations of each. Such familiarity is best gained by combining knowledge of the literature with the manner in which the techniques are actually applied (and their diagnostic yield) in the environment in which he practices. For example, even if contrast venography is reported to

be a reliable, sensitive technique in the literature, that fact is of little use if the procedure is either not available or subject to substantial technical-interpretive limitations when requested from a specific diagnostic service in a specific hospital.

KENNETH M. MOSER, MD

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Pulmonary Reactions to Drug Therapy

THE REACTIONS of pleuropulmonary tissues to drugs are increasing both in number and in variability of presentation. Although the mechanism involved in these reactions remains speculative, certain pharmacologic agents are more commonly associated with pathological conditions of the lungs.

Nitrofurantoin, a widely prescribed antibacterial agent, has been known for many years to cause both acute and chronic interstitial lung disease, pleural effusion and the pulmonary infiltrate with eosinophilia (PIE) syndrome. Recently, Bone and colleagues described the cases of two patients in which nitrofurantoin therapy was linked to the formation of desquamative interstitial pneumonitis. This disease may present as a predominantly alveolar pattern on roentgenograms of the chest. Both of their patients improved on discontinuance of the drug plus administration of corticosteroids. This reemphasizes the excellent prognosis for patients in whom the clinical entity of nitrofurantoin induced lung disease is recognized and the drug is discontinued.

A second widely prescribed drug, phenytoin (diphenylhydantoin), similarly has been shown to produce a variety of pulmonary reactions. Hilar adenopathy, acute and chronic interstitial lung disease, as well as miliary infiltrates all have been reported.

Hazlett has studied the loss of lung function occurring in patients receiving long-term phenytoin therapy. In 45 percent of their patients there were reduced steady-state diffusing capacities (DL_{CO}) and abnormal blood gas tensions for oxygen during exercise. In addition, in 50 percent of their patients there were widened resting alveolar-arterial oxygen differences or no increases in DL_{CO} with exercise, or both. The disturbing frequency of abnormalities, especially in younger patients, emphasizes the need to consider physiologic monitoring in order to follow and possibly prevent irreversible pulmonary disease in patients taking phenytoin.

Chemotherapy with cytotoxic drugs also is associated with pulmonary injury. Cytotoxic drug-induced lung disease, including both acute and chronic interstitial disease, hilar adenopathy, alveolar disease, pleural disease and lung carcinogenesis all have been reported. Methotrexate, busulfan and bleomycin have been the most commonly associated cytotoxic drugs.

Bleomycin, a drug with no major toxic effects on bone marrow or lymphoid tissue, has been known to cause interstitial pneumonia and pulmonary fibrosis in between 3 and 6 percent of patients. It is rarely seen in doses below 200 mg but death from pulmonary toxicity has been recorded in as many as 10 percent of patients who have received more than 550 mg. Therefore it would seem prudent to withdraw administration of the drug when symptoms, roentgenographic abnormalities or significant changes in pulmonary function occur. If infection is excluded and findings on pulmonary biopsy indicate bleomycin toxicity, the drug should be permanently discontinued.

Alarcon-Segovia has categorized drugs capable of inducing the development of systemic lupus erythematosus (SLE). Hydralazine, procainamide, phenytoin, isoniazid and chlorpromazine are among the drugs capable of inducing SLE in many persons receiving them for some time. In general, the clinical features of drug-induced SLE differ little from those of spontaneously occurring disease. However, pulmonary disease is much more common with the former.

Procainamide, an antiarrhythmic agent, and hydralazine, an antihypertensive agent, both widely prescribed, may produce pleuropulmonary disease. Indeed, 30 percent of patients with procainamide-induced SLE present with pleurisy whereas only 2.5 percent of spontaneously occurring SLE have symptoms referable to the lung. Additionally, serological differences also are present. Antinative deoxyribonucleic acid (DNA) antibodies do not occur in procainamide-induced

disease but have been reported with hydralazine-induced SLE. Discontinuance of these drugs has been associated with a high percentage of reversibility of disease.

Recognition that pulmonary injury may be secondary to many drugs is of great importance in preventing patient morbidity and mortality.

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The Staging of Lung Cancer: Clinical Benefits

TUMOR STAGING evaluates tumor size and location, the absence or presence and extent of lymph node or systemic metastasis, and tumor cell type. The techniques for staging lung cancer include physical examination, chest roentgenograms with hilar and mediastinal tomography, sputum cytology and isotopic scans. Bronchoscopy and mediastinoscopy are surgical methods for staging bronchogenic carcinoma.

The first benefit derived from staging has been the elimination of the unnecessary physical, emotional and financial cost of thoracotomy when that operation will not be beneficial. Therefore, patients with oat cell (small cell undifferentiated) carcinoma or contralateral mediastinal metastasis, whose survival will not be enhanced by surgical operation on the chest, are treated by other means.

The data from prospective and retrospective staging studies are beginning to aid clinicians in choosing and timing other forms of therapy for lung cancer. McKneally has done a randomized prospective study of patients with stage I tumors treated by resection and followed from one to three years. There were nine recurrences with death among the control group of 25 patients. Of 19 patients who were given intrapleural bacille Calmette Guérin (BCG) immunotherapy in the immediate postoperative period, there was only one patient with recurrence of tumor in the same period and all patients survived. Patients identified to have stage III lung cancer are showing improved survival with a combination of radiotherapy and multiagent chemotherapy (cyclophosphamide (Cytoxan®), doxorubicin hydrochloride (Adriamycin®), methotrexate and procarbazine).

How extensive should staging efforts be? In a patient with advanced lung cancer, x-ray studies of the chest, physical examination, and evaluation of symptomatic disease and immunocompetence (denitrochlorobenzine [DNCB] skin test) should suffice. For patients with malignancy in more confined stages, a group of informed and concerned cancer therapists should apply uniform diagnostic and treatment methods in the best known manner.

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EDITORIALS

An Alternative Approach to NHI

NOW SEEMS TO BE as good a moment as any to suggest an alternative approach to National Health Insurance (NHI). There appears to be an unexpressed but real reluctance to proceed with NHI at this time although there is a general consensus that a national program is necessary. The stated purposes of NHI are to assure that all our citizens have the basic medical and health care services they need and to control the escalating costs. The reluctance to proceed stems mostly from uncertainty about costs. This includes the costs of whatever services are to be paid for, the cost and cost effectiveness of the bureaucratic machinery which will be necessary to operate such a program, and the specter of federal controls restricting the quantity and quality of services to be rendered in order to control costs. There is also more than a suspicion that the administrative bureaucracy will be sluggish in response to local needs and technologic progress and that health care may become fixed at a level of mediocrity or worse. And finally the general public seems to place a lower priority on NHI than do many of our political leaders. A number of recent national polls seems to bear this out. Yet the pressures to do something are real enough. The present system of financing medical and health care services leaves much to be desired and is apparently unable to contain an unacceptable escalation in costs. Business and industry are now joining labor in pressing for NHI as a means of regulating the health care enterprise and thus controlling the cost of health care.

Everyone seems to assume that only the federal government with its massive bureaucracy can solve these problems. Yet the record of the federal government in diagnosing and treating problems such as this—and particularly problems in the health care delivery system—is not one to which anyone points with pride, and there is no precedent to suggest that there will be any better success with NHI, at least as it is presently conceived. So it seems reasonable to look for an alternative.

In analyzing the problem one can identify a political purpose, which is to assure equal access of all our citizens to basic emergency, preventive and definitive health care services. A corollary to the political purpose is an economic goal, which is to have the federal dollar commitment a reasonable and predictable one. And then there are social purposes: to have a system which will be responsive to local needs and local priorities in health care and which will reintroduce a healthy competition and cost consciousness into the delivery of health care services. And then, to be sure that things are working well, there will need to be some continuing surveillance or evaluation at the national level to assure that the basic services, as these may be defined, are indeed available to all citizens in a specified area, and at the local level to assure that the quality and quantity of services are appropriate and that local needs and priorities are being met.

It is suggested that two things will be needed to accomplish this: (1) dollars from the federal government to finance the federally mandated requirement that there be basic emergency services, basic preventive services and basic definitive services available to all, and (2) some kind of representative, responsible and responsive health care authority in each stated area to receive and administer these and other funds from other sources, and perhaps programs as well. In this proposal it is suggested that the federal dollars be in the form of capitation—so many dollars per person in a designated area, to be given in a lump sum to the health care authority in the area in return for providing for the basic services for all

citizens. Therefore it is suggested that an authoritative and responsible decision-making body be established in each such area to carry out the program. In a sense this area body might be viewed as a further extension of a concept that has been in place for some time—that health care decisions should be made in local areas by local agencies representing the community to be served. This concept has been evolving through: first the Regional Medical Programs (RMP), then the Comprehensive Health Planning (CHP) agencies, and most recently the Health Systems Agencies (HSA). But to be effective these bodies will need much more clout within their areas than has hitherto been the case. It is essential that *all* those who must carry out a plan also be part of the planning and decision making processes. There needs to be a community or area sense that it is their plan that they are carrying out so what is needed is something more like a "health alliance" which will actually involve all those groups and organizations that are properly concerned with medical and health care services for the area—a responsible agency or authority with real involvement of the providers and "doers" in the area as well as appropriate involvement of consumers and representatives of the underserved. Such an "alliance" could be the authoritative body to provide for the federal "basic" programs and to identify health care problems in the area and what is needed to deal with them, to decide what to do and then work together in the area to get it done.

How might this work? The area "alliance" would receive the capitation funds and make whatever arrangements were necessary to provide for the basic services required by the federal government. Many, perhaps even most, of these services are already in place. Others could be added. Contracts could be entered into by the "alliance" to buy services. Some areas might contract with others for services that could be more easily or more efficiently provided by them. Each area could decide what resources it might wish to add to the basic federal capitation funds in order to improve its health care system beyond the basic requirements for federal capitation. Savings from capitation dollars and funds from other sources could be used for this. In this way competition and cost consciousness could be made an integral part of the delivery system. Existing systems of payment could be used or modified as deemed necessary for efficiency and effectiveness. Federal surveillance would be limited to assuring that the basic services were indeed available to meet the minimum basic standards and to assure the funds were properly accounted for. Professional Standards Review Organizations (PSRO), also based in each area, could monitor quantity, quality and appropriateness of services, and the area "alliance" would evaluate its own programs, cost effectiveness and whatever, just as would any quasi-public business enterprise servicing a given area.

If an idea such as this is to be tried it should be thought through further by persons with expertise this writer does not possess. It should probably also be tried first experimentally in several different kinds of settings to see if it will work. But, if successfully implemented, it should (1) satisfy the political commitment to NHI, (2) put a reasonable and predictable limit on the federal dollars to be allocated to health care services and (3) place the incentives and responsibility for the delivery of health care services upon those who are properly involved in each designated area, which is where it really belongs in our free enterprise system. And this should not be all bad.

—MSMW

Peripheral Nerve Entrapments

YEARS AGO Kopell and Thompson grouped together a diffuse assortment of mononeuropathies, ascribed their cause to localized entrapment and published the now-familiar monograph *Peripheral Entrapment Neuropathies.*[1] The Specialty Conference moderated by Dr. Cracchiola, the proceedings of which appear in this issue of the WESTERN JOURNAL, is a refreshing review of the more common "entrapments." Anatomy, pathophysiology, diagnosis and treatment are outlined. Dr. Campion's succinct discussion of the electrodiagnosis of peripheral neuropathies should prove particularly helpful to the clinician.

The term "entrapment" is, in my opinion, a misnomer. Peripheral nerves are rarely trapped by surrounding tissue, nor is their function likely

to be disrupted because of capture.[2] However, these nerves are sometimes sufficiently compressed by surrounding tissue to cause impairment of nerve function by sheer mechanical force. The median nerve "trapped" in the carpal tunnel then becomes squashed, locally and repeatedly. Pathological specimens, electrophysiological data, and direct observation of nerve deformity at the operating table all confirm that the median nerve can be compressed by the transverse carpal ligament during flexion of the wrist. Similarly, repetitive trauma of the ulnar nerve, its intermittent subluxation across the medial epicondyle and certain anatomic features of the ulnar groove all contribute to produce a "tardy palsy." The pronator teres syndrome, caused by acute or chronic deformity and compression of the median nerve by fibers of the flexor sublimis muscle in the proximal forearm, is another example of a compression mononeuropathy. It may be argued that differences in meaning among the terms compression, mechanical force and entrapment are of merely semantic interest, with little clinical relevance. Yet, when decompression relieves signs and symptoms, compression per se must be acknowledged as the primary etiological factor.

A new clinical concept of peripheral neuropathies has evolved since the time when axoplasmic flow was first recognized. Simply stated, this hypothesis suggests that subclinical lesions in tandem may interfere with nerve function additively, to cause a neuropathy that is clinically indistinguishable from one produced by a single lesion.[3] For example, ulnar nerve compression at the elbow may cause a clinically obvious ulnar neuropathy to appear more rapidly in a patient with diabetic neuropathy than in one who is not suffering from diabetes also. Increasingly sophisticated electrodiagnosis can now identify the separate lesions, and has made precise treatment possible.

Some important facts about peripheral nerves and their responses to injury deserve emphasis here. First, most peripheral nerves have motor and sensory fibers. Hence, compression mononeuropathies cause both motor and sensory signs and symptoms, as a rule. Notable exceptions to the rule are the lateral femoral cutaneous nerve of meralgia paresthetica (a uniquely sensory syndrome), and the deep radial nerve of the posterior interosseus syndrome (exclusively motor). Most other compression neuropathies, including the ubiquitous carpal tunnel syndrome, tardy ulnar palsy and "Saturday night" palsy, involve mixed motor and sensory nerves.

Second, the more proximal the lesion, the wider the distribution of motor and sensory signs and symptoms. In the detection of the sites of nerve injury, it is clear that there is no better analytical tool than the physician's own specific knowledge of peripheral nerve anatomy.

Third, compression of a nerve proximally is not as well tolerated as compression distally. This is because axonal regeneration is more likely to occur when the initial injury is distant from the cell body. Therefore, decompression of a nerve that is compressed distally, rather than proximally, is more apt to be effective.

Fourth, the longer a nerve is compressed, the less likely it is that decompression will result in any improvement.[4]

Transsection or avulsion of a nerve to treat compression neuropathy is rarely necessary. Motor loss following section of a mixed nerve is usually too high a price to pay for transient improvement of a sensory complaint. Occasionally, transsection of the lateral femoral cutaneous nerve for intractable meralgia paresthetica is effective, but more often it is not. "Never cut a nerve" is a time-honored admonition of wise and experienced neurosurgeons. The adage is particularly appropriate in compression neuropathies, for transsection usually changes a simple problem into a more complex one.

Compression mononeuropathy or peripheral entrapment neuropathy should be diagnosed sparingly and by exclusion. Frequently the neuropathy reflects one minor aspect of a larger problem, such as acromegaly, myxedema, rheumatoid disease, amyloidosis and the like. Treatment of the systemic disorder may cure the neuropathy. Similarly, mononeuropathies are often caused by specific lesions strategically placed—a malaligned fracture, a neoplasm within or adjacent to the nerve, or a prior traumatic injury. Sometimes the neuropathy is self-induced, as in meralgia paresthetica caused by pressure from a heavy gun belt, or a carpal tunnel syndrome resulting from the improper use of crutches. Occasionally, neuropathies result from compression by normal body structures, as in the pronator teres syndrome which follows sudden, forceful contraction of the flexor muscles in the forearm, or the carpal tunnel syndrome which occurs in stenographers and jack-

hammer operators. This last group of lesions, the normal anatomy group, is interesting as well as easy to remember. More difficult to diagnose are the widely varying types of lesions that can cause "entrapment" (compression) neuropathies; their identification and successful treatment continue to present a significant challenge.

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Today's New Physicians

Dr. Richard G. Swanberg discusses "The Medical Challenge of Coping with Stress" elsewhere in this issue. The occasion was his address as a graduating medical student at the 23rd Annual Hippocratic Oath Ceremony at the University of California, Los Angeles, School of Medicine, in June of this year. It comes through that for this generation of medical students the stresses of becoming a doctor are much the same as for previous generations, and so is the idealism and grit that it takes to cope and to achieve the goal. The goal is now, as before, to become a quality physician well trained to care for patients, to understand and show compassion for fellow human beings who are under stress, and to "look at the whole patient and not just his disease." And the needs of society are not being overlooked. Three quarters of the graduating class plan to enter one of the primary care specialties "in which a physician is best able to treat the entire patient." All of this should be more than reassuring to legislators and others, in and out of the profession, who have been concerned about the goals and attitudes of today's new physicians. We can welcome these young doctors to our ranks.

—MSMW

Angiotensin Converting Enzyme Levels in Sarcoidosis

Sarcoidosis is a multisystem granulomatous disorder of unknown cause. The disease has a worldwide distribution. In the United States its incidence is estimated at about 30 to 40 per 100,000 of population. Although generally considered a benign disorder, sarcoidosis carries a mortality rate of 5 percent.[1] As a general rule the diagnosis of sarcoidosis is considered secured if all of the following criteria are satisfied: (1) compatible clinical or radiological features, (2) evidence of noncaseating granulomas in one or more organs and (3) negative bacterial and fungal studies of biopsy tissue specimens to rule out other specific causes of granulomatous disease. If all three steps are not carried out the diagnosis of sarcoidosis remains in doubt since clinical or radiological features present too wide a differential diagnosis and histological evidence of noncaseating granulomata may be produced by many bacteria, viruses, fungi and chemicals.[2]

Strict adherence, however, to this three-step diagnostic workup presents two major practical problems. First, the patient, particularly when asymptomatic, may not be willing to have an invasive procedure carried out. Second, biopsy procedures, depending on the site and technique used, carry definite risks of morbidity and even mortality. Consequently for many years the Kveim-Siltzbach test has been identified as another diagnostic test.[3] The test is done by injecting validated suspension of human sarcoidal tissue intradermally in the forearm. In about four to six weeks a tiny nodule appears in about 75 percent of patients with active sarcoidosis. Findings on a biopsy of the nodule show noncaseating granulomas. However, since the Kveim-Siltzbach antigen is not available commercially, the test unfortunately is of no use to practicing physicians.

Recently Lieberman reported a new serological test for sarcoidosis.[4] He found that 83 percent of patients with active sarcoidosis have abnormally high levels of angiotensin converting enzyme (ACE) in the serum. The highest ACE levels were found in persons with bilateral hilar lymphadenopathy and pulmonary infiltrate (stage II sarcoidosis). Resolution of the active disease or

clinical control of sarcoidosis by adequate doses of corticosteroids brings the serum ACE level down within the normal range. Dr. Lieberman also reported that no other disease state involved in the differential diagnosis of sarcoidosis was found to have elevations of serum ACE activity. Similar observations were made by other workers.[5] However, when Fanburg and co-workers measured ACE activity in their patients with sarcoidosis, abnormally high levels were found in only 48 percent. The authors also noted that in 9.5 percent of patients with tuberculosis and lymphomas —two conditions commonly involved in the diagnosis of sarcoidosis—ACE activity was significantly high.[6] Lieberman and Rea later reported that in 72.5 percent of patients with leprosy there also were high serum ACE levels.[7] Silverstein and associates note that a statistically significant elevation of serum ACE occurs in only 34 percent of sarcoidosis patients. They found the test of value in differential diagnosis but did not perceive any difference between steroid-treated and untreated patients.[8] It is possible that elevated serum ACE levels reflect enzyme secretory activities by epithelioid cells of the sarcoid granuloma.

In summary, serum angiotensin levels, if significantly high, provide diagnostic help in those cases of sarcoidosis in which there is clear clinical or radiological evidence of the disease. Further studies are needed to establish usefulness and limits of the test in securing the diagnosis and evaluating the course of the disease. Meanwhile the diagnosis of sarcoidosis should be considered established if the clinical and radiographic features are augmented by evidence of noncaseating granuloma and if specific bacterial and fungal disorders have been excluded by appropriate laboratory and immunologic tests.

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Medicine and the Quality of Life

QUALITY OF LIFE increasingly is being identified as a goal of medicine and health care. In the July 1976 issue, the editors began a forum for discussing the actual and ideal relationships between medicine and the quality of life by printing seven articles expressing differing views. A number of comments generated by those articles were printed in succeeding issues. A summary of the dialogue appeared in the June 1977 issue.

Readers are invited to take part in a continuation of this forum by submitting their comments, written as succinctly as possible. As many of these as space permits will be published in future issues.

Unloving Care

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Dying isn't everything;
one must die in time.
JEAN PAUL SARTRE

I WOULD EXPECT many of my readers to disagree with my suggestions. I ask you, therefore, "to accept every assertion I make as a question."[1]

The ethics that have guided my reflections on this subject are those espoused by Joseph Fletcher (Robert Treat Paine Professor of Social Ethics, Episcopal Theological School, Cambridge, Massachusetts; visiting Professor of Medical Ethics, University of Virginia, 1971).

Forty years of direct patient care, 30 as a family doctor, is the stimulus for these comments, which are concerned with senile patients, *not* with those moribund or terminally ill. I wish to focus attention on patients with organic brain disease so far advanced as to make permanent confinement to a nursing home mandatory. They are easy to identify: they would score less than 10 on the Cognitive Capacity Screening Examination.[2]

These are patients we all have seen scores of times and ones many of us in family practice see weekly on our nursing home visits. The total number of these patients and their percentage of our population is increasing yearly. That is why nursing homes are considered a good place to invest money. There are 1,000,000 Americans so confined today.

The problems these patients present will not just go away. Advancing medical science and technology, increasing length of life, and smaller families and smaller homes guarantee an ever increasing amount of suffering for senile patients requiring custodial care. It is my thesis that the medical professional magnifies this problem by what is called "good medical care."

The patients I have in mind are totally beyond any rehabilitation. They do not know the year, the month, the season or the time of day. They barely know who they are, or where they are. They do not know the name of the President of the United States or the governor of their state. Often they do not know their family. They can not add 2 and 2 or subtract 1 from 3. They cannot read a headline with understanding and cannot talk except in simple repetitive phrases. Frequently, their hearing and their vision as well as their understanding are grossly impaired. Few have bladder control, many need a Foley catheter, or adult diapers. Not a few have no more bowel control than an infant. Many are bedfast. Few can bathe or dress themselves. Hardly any can walk normally.

However, when the charge nurse in the nursing home calls their doctor to report that one of these patients has a *febrile* respiratory or urinary infection, unless the patient is moribund or terminal, nine times out of ten, in the name of good medical care the doctor will prescribe a course of antibiotics to cure the complications. He will frequently order long-term small doses of antibiotic to prevent a recurrence.

In addition, a large number of these patients are receiving daily doses of digitalis and diuretics to prevent heart failure. Some are fed by nasogastric tube. I do not believe all this is preserving "life" if one means by this word the "total personal being—body—mind—spirit."[3] Rather, these "doctor's orders" prolong the act of dying, and I believe this to be *unloving care*.

I believe that cerebral arteriosclerosis of the type I have tried to describe is just as progressive, just as incurable and just as terminal as far advanced metastatic carcinoma. However, today, unfortunately for the patient, advanced senility takes much longer to cause a natural death, thanks to medical progress.

I believe that when we cannot cure our patients, it is our duty to try and relieve their suffering, not prolong it. I am opposed to any type of positive euthanasia but I am in favor of *effective* negative euthanasia for the type of patient under consideration. This takes more courage than "standard routine treatment" in this day of malpractice suits. However, I agree with Dr. Jaretzki who says: "I think the doctor has a great responsibility to act *positively* in a negative way in solving this problem."[4] I think that three years of medicated existence in a nursing home *increases* the patient's suffering.

It is my belief that even the simplest most common and most "routine" of *modern* antibiotics and diuretics (as opposed to those available when I was an extern at Presbyterian Hospital in Chicago 40 years ago), are so effective and so powerful as to make their use "unloving care" and poor medical treatment in any except the scientific calculative meaning of the word "treatment."

Joseph Fletcher in *Situation Ethics*[5] states: "Only one 'thing' is intrinsically good, namely, love; nothing else at all." He also states: "There is only one thing that is always good and right, intrinsically good regardless of context, and that one thing is love." And he says: "Unlike all other principles you might mention, love alone when well served is always good and right in every situation. Love is the only universal." Dr. Fletcher defined this type of love (agape) "as good will at work in partnership with reason."

Refer to: Baer LS: Unloving care, *In* Medicine and the quality of life—A forum. West J Med 127:338-339, Oct 1977

Using my understanding of Dr. Fletcher as my guide, *I propose* that it should be considered *good medical practice* to let this type of patient die a natural death when infection or heart failure comes as "their friend." I propose that *good care* of the inevitable respiratory infection in a patient with far advanced arteriosclerotic brain disease be cough relief, sedation and good nursing care, not the use of antibiotics.

I propose that *good care* for the inevitable urinary tract infection be ample fluids, phenazopyridine (Pyridium®) or some other analgesic and aspirin—not antibiotics. (For high fever a tepid sponge or a warm alcohol rub would contribute to the patient's comfort without prolonging existence.)

I propose that neither digitalis nor diuretics be used, in advanced senile patients, for congestive heart failure. Rather, therapy with meperidine (Demerol®) in frequent 50 or 75 mg doses should be considered good care and the treatment of choice for cough, dyspnea, orthopnea or restlessness.

If "the proper function of man is to live, not to exist,"[6] then I believe that the common practice of treating nursing home patients suffering from advanced senility with antibiotics, diuretics and digitalis is "unloving care" and should cease to be considered "good medical practice."

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The Pill and Gonorrhea

The birth control pill is an effective contraceptive drug. It has a specificity in excess of 99 percent. It works. It has side effects like most drugs and these side effects are what affect us in venereology. Because of estrogen, there is a stimulation of the cervical glands and the cervical glands pour out secretions. And a girl taking the pill is always moist. The cervical secretions are alkaline and they tend to neutralize the normal acid of the vagina. Estrogen stimulates carbohydrate production in the vagina. So we have food, we have body temperature, we have all the growth and survival requirements of the gonococcus . . . .

If a woman was exposed to a man with gonorrhea and she used nothing—no pill or anything else—her chances of being infected from one exposure with that man are 40 percent. On the other hand, if she were taking the pill and was exposed to that same man with gonorrhea, her chances of the disease developing approximate 100 percent . . . . Now, don't mistake what I said, I didn't say the pill causes gonorrhea. All I said is that a girl who is taking the pill and is exposed to a man with gonorrhea has an increased chance of getting infected.

—NICHOLAS J. FIUMARA, MD, *Boston*
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CASE REPORTS

Refer to: Cohen R, Mackey K: Hymenolepis diminuta unresponsive to quinacrine. West J Med 127:340-341, Oct 1977

Hymenolepis diminuta Unresponsive to Quinacrine

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CLINICAL INFECTION by Hymenolepis diminuta, the rat tapeworm, is an uncommon event in the western United States. However, because of increasing numbers of immigrants into the United States from endemic areas such as Mexico and Latin America; because H. diminuta infection is often subclinical, and because reporting H. diminuta infection is not required by law in most states, this disease may be of greater significance than presently recognized. The case described illustrates not only the clinical presentation of H. diminuta infection, but also problems in its treatment.

Report of a Case

On November 5, 1975, a 9-year-old Mexican-American girl was referred to the local health department by her family physician for treatment of Hymenolepis diminuta. The patient had emigrated from Mexico in 1972 and at that time noted the onset of episodic periumbilical abdominal pain usually occurring after meals and lasting 10 to 20 minutes. These episodes were often accompanied by vomiting and occasionally by an unformed black stool. The patient also had daily episodes of headache with diaphoresis, chills and abdominal distention. She was seen by her family physician who ordered a study of stool specimens for ova and parasites; H. diminuta eggs were found. Over the next three years the patient was treated with four separate courses of quinacrine (Atabrine®) without cure.

Upon referral to the health department in 1975, the patient said that she had lost no weight and that she felt well except for a vague abdominal discomfort. Other past medical history was unremarkable, and the patient's parents and siblings were in good health. The patient's temperature was 37.6°C (99.7°F), pulse 100, weight 28.6 kg and height 124 cm. The remainder of the findings from the physical examination were unremarkable. A study of stool specimen showed the presence of eggs of H. diminuta. The hematocrit was 36 percent, and the leukocyte count was 9,000 cells per cu mm with 36 polymorphonuclear leukocytes, 3 bands, 55 lymphocytes, 3 monocytes, 2 eosinophiles and 1 basophil. The Parasitic Disease Drug Service at the Center for Disease Control graciously provided niclosamide (Yomesan®)* tablets, and therapy was begun on November 18, 1975. The patient was given 1 gram the first day followed by 0.5 grams per day for six days. Following completion of therapy the patient felt better, was afebrile and denied recurrence of abdominal pain. Negative stool specimens were obtained on the first day of treatment and one week following completion of treatment; however, the three month stool specimen contained H. diminuta eggs.

On April 6, 1976, the patient was reevaluated. Her weight was 32.2 kg, and a second course of niclosamide was started at the increased dosage

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Submitted, revised, October 26, 1976.

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*Niclosamide is manufactured in Germany and not marketed in the United States. It is obtainable by licensed physicians from the Parasitic Disease Drug Service, Center for Disease Control, Atlanta, GA 30333.

schedule of 1.5 grams the first day followed by 1 gram daily for six days. The patient's only complaint of side effects during either course of niclosamide therapy was occasional abdominal cramping (relieved by bowel movement). Following the second course of therapy the patient continued to gain weight without recurrence of abdominal cramping. Tests of stool specimens after one week, one month and three months were negative for H. diminuta eggs.

Discussion

Rodents are the definitive hosts of H. diminuta. Eggs are excreted in the rodent feces and subsequently ingested by arthropods (millipedes, beetles, earwigs, rat flea larvae and others) in whom larval stage development occurs. Rodents then ingest infected arthropods to complete the worm's life cycle. Most reported human infections have been in children who are infected by eating parasitized arthropods, which are usually ingested as grain and cereal contaminants. Protection of food storage from both insects and rodents in the United States has prevented widespread human infection, although human infection has been reported in several states, particularly in the Southeast.[1]

Although most human infections are asymptomatic, the case presented illustrates its clinical presentation and course which may include weight loss, anorexia, nausea, vomiting, abdominal pain and diarrhea. Diagnosis is made by finding the characteristic eggs or proglottids in the patient's feces. This report underscores the value of stool examination for ova and parasites in immigrant children from endemic areas who have gastrointestinal complaints.

Until recently quinacrine provided the most effective treatment; however, the availability of niclosamide, a more effective agent for most tapeworm infections, has enabled definitive cure in more resistant cases such as this.

Summary

This case report of a child clinically infected with the rat tapeworm, Hymenolepis diminuta, describes (1) a disease rarely diagnosed in the western United States and (2) the use of niclosamide to cure the infection.

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Refer to: Haddad JK, Doherty C, Clark RE: Acute gastric volvulus—Endoscopic derotation. West J Med 127:341-346, Oct 1977

Acute Gastric Volvulus—Endoscopic Derotation

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GASTRIC VOLVULUS is a rare, acquired condition in which the stomach rotates upon itself. Bockus,[1] in his second edition (1974), noted that there had only been 277 cases reported in the literature at that time, this number including cases of both acute and chronic volvulus. Acute gastric volvulus presents as an abdominal emergency with a high mortality rate, and usually requires immediate surgical therapy. This report describes the case of a 52-year-old woman who presented with acute gastric volvulus. After gastric decompression by nasogastric tube, the volvulus was derotated with a fiberoptic endoscope. Clinical and radiologic features in acute gastric volvulus are characteristic. Use of modern therapeutic techniques should improve treatment of this condition.

Report of a Case

A 52-year-old woman, who had been in excellent health without previous gastrointestinal symptoms, was admitted to hospital because of severe abdominal pain. The night before admission she had a small amount of Mexican food with a cocktail but did not overeat. Shortly thereafter she noted the onset of severe abdominal pain followed by repeated bouts of retching without being able to vomit. Her pain became progressively more severe and she noted abdominal distention. She was seen in the emergency room at 2 AM, eight hours after the onset of symptoms, in excruciating pain and was admitted at that time.

Her past history was unremarkable. She smoked and drank alcohol in moderation and took no medications. Family history and review of systems were unremarkable.

When first examined the patient was in excruciating pain, unrelieved by an intramuscular

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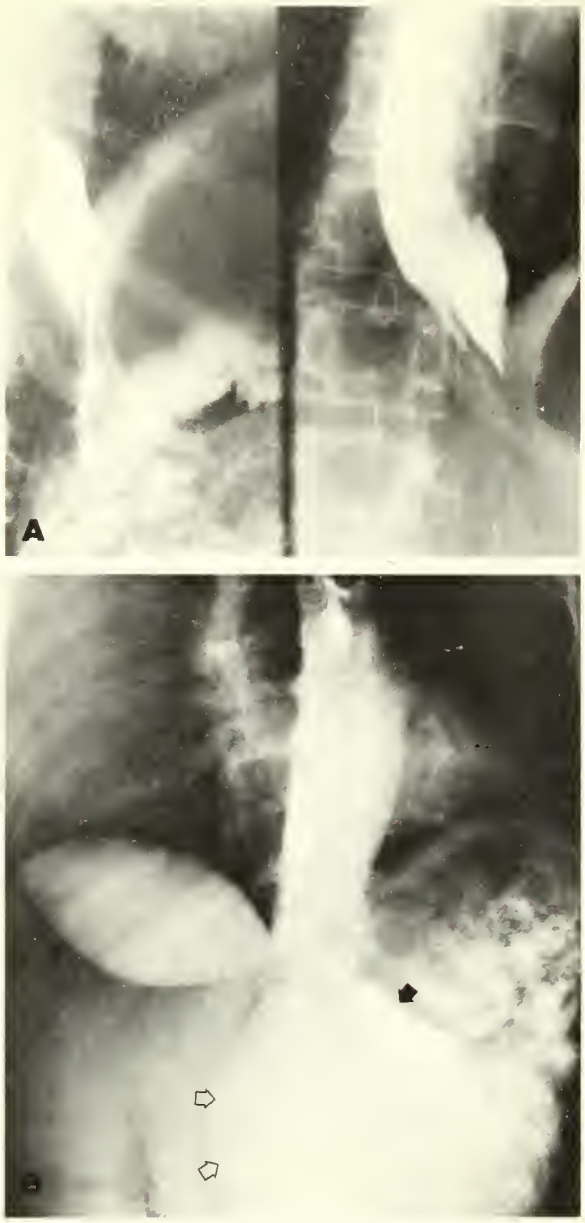

Figure 1.—A, Spot films of the barium filled esophagus show a beak-like termination of the esophagus at the esophagogastric junction. Gas in the massively dilated gastric fundus is noted superiorly and diluted barium is noted in the dilated stomach inferiorly. **B,** Upper gastrointestinal series in the right posterior oblique projection shows the beak-like termination of the esophagus. The massively dilated stomach is outlined by diluted flocculated barium. The greater curvature is delineated by open arrows and the antrum by a closed arrow. Note the complete obstruction at the pylorus was evidenced by no passage of barium distal to this point.

injection of 75 mg of demerol. Blood pressure was 150/90 mm of mercury and pulse was 110. Moderate dehydration was present, otherwise the ear, nose and throat examination showed no abnormalities. There was no adenopathy. The heart and lungs were normal. Examination of the abdomen was difficult because of the exquisite tenderness. There appeared to be a hard, tender, tympanitic mass in the left upper quadrant. Bowel sounds could not be heard.

Results of complete blood count, urinalysis, electrolytes and Sequential Multiple Analysis (SMA-12) panel were unremarkable. On x-ray studies of the abdomen a huge left upper quadrant mass was seen with a large air-fluid level consistent with massive gastric dilatation. Upper gastrointestinal examination showed a dilated esophagus with high grade obstruction at the cardioesophageal junction. The distal esophagus had a tapered beak-like configuration with twisted thickened mucosal folds (Figure 1A and 1B). A small amount of barium entered a massively dilated stomach which was completely obstructed at the pylorus. The dependent position of the greater curvature was characteristic of mesentero-axial gastric volvulus.

Under fluoroscopic observation, a nasogastric tube with an opaque marker (Salem Sump®) was carefully passed into the stomach. More than 2,000 ml of gastric contents were aspirated. Immediately following decompression the patient became quite comfortable and the abdomen became soft and nontender. Fluoroscopic examination indicated that there was still considerable residual material remaining in the stomach and that the volvulus had not been derotated.

Shortly following this procedure the patient was premedicated and upper gastrointestinal endoscopy, utilizing the Olympus® GIF forward-viewing panendoscope, was carried out. Barium and debris were present in the dilated esophagus. The distal half of the esophageal mucosa appeared dusky in color and edematous with thickened longitudinal ridges going down the esophagus. At 35 cm from the lower incisor teeth the lumen was pinched off by a twisting effect of the longitudinal folds going into the esophagogastric junction. With careful manipulation and gentle pressure the instrument was passed through this narrowed, twisted area and into the gastric cavity. This cavity was full of retained secretions and some barium, much of which was aspirated through the endoscope. The instrument was manipulated in all directions and a huge gastric pouch could be discerned. Mucosa was edematous and dusky in appearance, with punctate hemorrhagic areas seen throughout. All of the stomach seen appeared to be fundic tissue

Figure 2.—Upper gastrointestinal series done two days after derotation of the gastric volvulus shows normal stomach and duodenal position.

with large folds being present. No normal gastric anatomy could be discerned and the stomach appeared to end in a blind pouch where the other end of the twist was felt to be present. The instrument was then manipulated into a "J-shape" and repeated attempts at rotating the instrument in a counterclockwise direction proved to be of no avail. Counterclockwise rotation of the instrument had been previously planned after review of the x-ray films led us to believe that the volvulus had been an anterior type of clockwise type of rotation. The instrument was then rotated in a clockwise direction and with a sudden maneuver the volvulus was observed to derotate, suggesting that this had been a posterior or counterclockwise type of rotation. Immediately, normal stomach anatomy could be appreciated and the entire stomach was then carefully examined. The fundus, antrum and pylorus were all normal and the instrument was easily passed through the pylorus into the duodenum, which was normal. The cardioesophageal junction and esophagus were noted to be normal as the instrument was withdrawn. No hiatal hernia was seen.

The patient was observed in the hospital for 48 hours and was then discharged completely asymptomatic. Upper gastrointestinal roentgenograms before discharge showed a normally positioned esophagus, stomach and duodenum (Figure 2). The patient was told that acute gastric volvulus could recur. Elective operative fixation of the stomach was advised, but the patient did not wish to undergo any further therapy at that time.

The patient has remained well and when last interviewed four months following discharge she described no subsequent gastrointestinal symptoms.

Discussion

Gastric volvulus was first described at autopsy by Berti in 1866. The first successful surgical treatment was reported by Berg in 1897. Since that time less than 300 cases of gastric volvulus, including both acute and chronic presentations, have been reported. The classification of this rare condition was proposed by Von Haberer in 1912 and was modified by Singleton[2] (see Table 1).

Ligamentous relaxation is a major factor permitting volvulus to occur. The degree of rotation is variable, but in total volvulus it varies from 180 degrees to 360 degrees.[8] Partial volvulus usually involves rotation of less than 180 degrees. Cole[9] suggests that "volvulus" should be reserved for complete or total obstruction and that "torsion" should be reserved for those that are less than complete or are chronic.

Acute total gastric volvulus presents as an acute condition of the abdomen. There is sudden onset of epigastric pain which rapidly becomes very severe. Vomiting may be present initially, but is soon replaced by persistent retching without emesis due to the cardioesophageal obstruction. Distension of the upper abdomen soon develops with the appearance of a mass usually in the left upper quadrant, which may be tympanitic (closed-loop obstruction). The lower abdomen is often flat and nontender. Because of its excellent blood supply, the stomach is able to tolerate the pronounced degree of torsion and congestion of gastric tissues which develops.[10] The blood vessels are rarely obstructed sufficiently to cause early necrosis or gangrene.[9,11] Vascular compromise with necrosis and shock may occur with death ensuing, however, if the patient remains untreated. With treatment, the mortality for this condition has been reported to be from 30 to 50 percent. These figures come from the older literature and certainly early surgical therapy under modern conditions is probably associated with a much lower mortality. Consequences of acute volvulus include perforation,[12,13] hemorrhage,[14] acute gangrene[8,11] and splenic rupture.[15] Borchardt[16] in

TABLE 1.—*Classification of Gastric Volvulus*

Type (rotational axis)

Organo-axial. Rotation of the stomach on its longitudinal axis or cardiopyloric line, either right to left or in the opposite direction.

Mesentero-axial. Rotation of the stomach about its transverse axis or the line connecting the middle of the lesser curvature with the middle of the greater curvature.

Mixed. Combination of the two types. Mesentero-axial rotation can predispose the stomach to further twisting in an organo-axial direction.

Extent

Total. Complete rotation of the stomach, usually associated with gastric dilatation and obstruction.

Partial. Rotation is limited to a segment of the stomach, usually the pylorus. Acute obstructive symptoms are less common.

Direction

Anterior. The transverse colon comes to lie in front of the stomach. Rotation is in a clockwise direction and is the most common type.

Posterior. The transverse colon must pass behind the stomach, in counterclockwise direction, elongating or tearing the meso-colon.

Severity

Acute form. Presents as an upper abdominal catastrophe resulting from obstruction or strangulation.

Chronic form. Presents with recurrent or persistent and invariably confusing symptoms, or may be asymptomatic.

Cause

Idiopathic. In a third of cases, no associated disease or abnormality is noted. Relaxation of the ligamentous support of the stomach is essential for development of volvulus, that, is, weakness of the gastrohepatic, gastrocolic or gastrosplenic ligaments.[3,4] Acute dilatation of the stomach, hourglass stomach, trauma, intractable vomiting, increased intra-abdominal pressure such as is seen in pregnancy, and exaggerated peristaltic activity are some of the precipitating factors that have been described.[3]

Secondary. Most cases can be related to demonstrable intra-abdominal disease which can be intragastric or extragastric in origin.[5] The most common causes are hiatal hernia, eventration of the diaphragm, benign or malignant tumors of the stomach, paragastric adhesions, and chronic gastric ulcers. Rarer causes include chronic duodenal ulcer, splenomegaly, distended colon and phrenic nerve injury. Cases have also been reported in patients with congenital absence of the left lobe of the liver[6] or with resected left lobe of the liver,[7] as well as after pneumonectomy or lower lobectomy.

1904 described a diagnostic triad for acute gastric volvulus, which has been widely quoted: (1) inability to vomit with retching; (2) upper abdominal distension; (3) inability to pass a tube into the stomach.

The diagnosis may be difficult but is suggested in a patient with an acute condition of the abdomen if the above features are present, although Borchardt's third criterion is not invariably present. Radiographic findings of acute gastric volvulus are diagnostic.[17] Plain films of the abdomen may show a left upper quadrant mass with air-fluid levels. A left upper quadrant double fluid level, when seen, is suggestive of the diagnosis. Immediate upper gastrointestinal examination will confirm or exclude the diagnosis of gastric volvulus. The esophagus may be dilated with a beak-like appearance at the obstructed cardioesophageal junction. Twisting of edematous esophageal folds may also be present. If barium traverses the esophageal obstruction, the massively dilated stomach will be visualized in a twisted position usually with gastric outlet obstruction. A beak-like appearance of the gastric antrum may be visualized. Identification of the greater curvature of the stomach adjacent to the diaphragm is characteristic of organo-axial volvulus. The gastric antrum in a pronounced superior and anterior position identifies the mesentero-axial type. Angiography[18] may be helpful in the diagnosis of chronic gastric volvulus but would appear unnecessary in acute volvulus.

Patients with acute gastric volvulus require immediate treatment; death usually results if patients are not treated. Surgical mortality has been high and probably relates to delays in diagnosis and treatment. Although spontaneous resolution of acute partial volvulus has been reported,[19] these cases were not associated with total volvulus and complete obstruction. Nasogastric decompression alone has resulted in derotation of a volvulus and has been recommended as sole treatment. Recurrent acute volvulus following decompression alone has occurred, however, and definitive surgical therapy is usually recommended.[4] It has been stated that a tube often cannot be passed into the stomach, and because cases of perforation of the esophagus and of the stomach have been attributed to "blind" gastric intubation,[3,9] this procedure has been felt to be dangerous. Tubes have been passed into the stomach, however, with dramatic improvement in symptoms following aspiration of gastric contents.[3,20] Relief is only temporary, however, and the stomach rapidly distends again when aspiration is discontinued. With the advent of radiopaque marked tubing and image-intensification fluoroscopy, it would seem that gastric intubation should be immediately attempted in cases of acute gastric volvulus.

The historical surgical teaching for the manage-

ment of acute gastric volvulus has been immediate laparotomy.[16] The usual surgical maneuvers have included decompression of the stomach with a trocar and untwisting of the volvulus. In idiopathic cases, suturing the entire gastrocolic and gastrosplenic ligaments to the peritoneum of the anterior abdominal wall with nonabsorbable sutures is a safe method of gastropexy to prevent recurrent volvulus.[2] The gastrocolic and gastrosplenic ligaments are sutured along a wide arc from the lower pole of the spleen to the pylorus. The stomach is fixed in its normal position so as not to be angulated by changes in the patient's position. The fixation is without gaps to prevent the possibility of intestinal obstruction. Shortening of the gastrohepatic ligament and gastrostomy are unnecessary. In secondary cases, surgical correction is directed to the primary cause, if the patient's condition permits. This may include gastric resection or procedures to repair a hiatal hernia or eventration of the diaphram. The recommended operation in patients with eventration of the diaphragm is colonic displacement of the stomach.[22] The greater curvature of the stomach is completely freed from the colon so that the transverse colon and greater omentum can roll up under the left diaphragm without twisting the stomach. A gastropexy is also done.

Endoscopy has not been previously reported in any patient with total acute gastric volvulus. The gastroscope was utilized once,[23] apparently to derotate a partial volvulus. It has been stated that fiberoptic endoscopy should play little role in this condition since the twist precludes passage of the instrument.[24] This case is instructive in that it appears to be the first reported instance in which an acute total volvulus of the posterior mesenteroaxial type was derotated endoscopically. Definitive surgical fixation of the stomach was advised, but further treatment was not desired by the patient. Recurrent acute volvulus certainly remains a possibility in this case.

In light of the present case, a more contemporary approach to the management of this rare condition is suggested. Clinical suspicion of acute gastric volvulus should be confirmed by emergency upper gastrointestinal x-ray studies, followed by attempted passage of a radiopaque nasogastric tube under fluoroscopic control. If successful, gastric decompression should then make the patient comfortable and remove the urgency of the situation. Intravenous fluid replacement and sedation can be initiated, and if possible the colon should be evacuated with enemas. The patient can then be prepared for fiberoptic endoscopy. This should be done as soon as feasible, with the understanding that endoscopy under conditions of vascular compromise of the gastric tissues must be contemplated with care. The risks of mucosal injury or perforation are probably greater than under usual endoscopic conditions and great caution should be used. Certainly not all cases of volvulus may be amenable to endoscopic derotation. If the stomach can be entered, then endoscopic derotation should be cautiously attempted. If derotation is successful, the situation is then no longer critical and further confirmation with contrast radiography is possible. Definitive surgical procedures to prevent recurrence of volvulus can then be done under controlled elective conditions and after the previously engorged gastric tissues have returned to normal.

Failure to intubate and decompress the stomach in acute total volvulus constitutes a grave surgical emergency. Because of the consequences of vascular compromise to the stomach, surgical operation should be carried out immediately if decompression has not been successful.

Summary

A 52-year-old woman presenting with severe abdominal pain was found by radiographic studies to have an acute total gastric volvulus. Decompression of a massively dilated stomach was possible after a radiopaque nasogastric tube had been passed into the stomach under fluoroscopic guidance. Fiberoptic endoscopy was done and derotation of the volvulus was successfully accomplished with the endoscope, thereby obviating the need for immediate surgical intervention. Subsequent upper gastrointestinal x-ray studies showed no abnormalities. The patient refused definitive surgical fixation and has remained well without further gastrointestinal symptoms. The clinical features and radiographic findings in this rare condition are described and a contemporary therapeutic approach is suggested.

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Acute Pulmonary Cavitation in Sarcoidosis

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SARCOIDOSIS IS A relatively common multisystemic disorder whose cardinal findings are most frequently pulmonary and consist of bilateral hilar adenopathy or diffuse pulmonary fibrosis, or both. The purpose of this report is to present a rare manifestation of sarcoidosis: pulmonary cavitation.

Report of a Case

A 31-year-old black woman presented to the hospital with cough, sharp pain on the left side of the chest and dyspnea. A chronic cough had been present for a year, producing small to moderate amounts of whitish to yellowish sputum. She had lost eight pounds in the four months before admission. The patient said that there had been no fever, chills, night sweats, skin rash, arthralgias, or cardiac or renal problems. One year before admission she had been admitted to another hospital for delivery of her second child. At that time, an abnormality was noted on a chest x-ray film which was felt to be consistent with pulmonary tuberculosis. Sputum mycobacterial cultures were negative. The patient was given isonicotinic acid hydrazide, ethambutol and streptomycin. After two months she was lost to follow-up. She was followed at another clinic for hypertension and took alphamethyldopa and hydrochlorothiazide until five months before the present admission.

On physicial examination at admission the patient appeared chronically ill and was in mild respiratory distress. Temperature was 102.8°F (39.3°C) orally; pulse, 160 per minute; respirations, 44 per minute and labored; blood pressure, 160/100 mm of mercury. Breath sounds in the left side of the chest were decreased and moderate tenderness in the abdominal right lower quadrant was noted. Results of the examination were otherwise unremarkable.

The leukocyte count was 11,000, with a mild left shift of the differential count. Analysis of urine showed no abnormalities. The serum glutamic pyruvic transaminase value was 50 (normal, 5 to 40 units) and the serum glutamic oxaloacetic transaminase value was 70 (normal, 5 to 40 units). The rest of the liver function studies, electrolytes and renal function studies showed no abnormalities. Gram stain of the sputum showed moderate numbers of polymorphonuclear leukocytes and Gram-positive cocci. A few Gram-negative rods were also noted. Sputum cultures showed normal aerobic flora. Fungal and mycobacterial cultures were negative. A transtracheal aspirate study showed the presence of anaerobic streptococcus, diphtheroids and bacteroides melaninogenicus. Tuberculin, histoplasmin and coccidioidin skin tests were negative. However, there was a 5 mm induration for mumps skin test. The serum immunoelectrophoresis showed slight elevation of IgA.

An x-ray film of the chest (Figure 1) showed a left pneumothorax. A chest tube was placed. During the ensuing two-month hospital stay, the patient had a stormy course, marked by fever and continued pulmonary cavitation (Figure 2).

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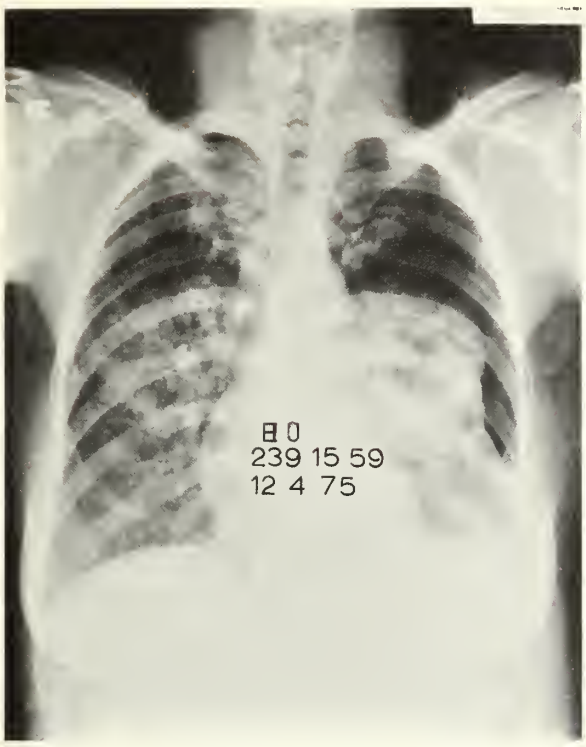

Figure 1.—Posteroanterior chest roentgenogram showing diffuse reticular, linear and nodular infiltration in both lungs with pneumothorax on the left. Note the rarifaction in the center of the collapsed lung.

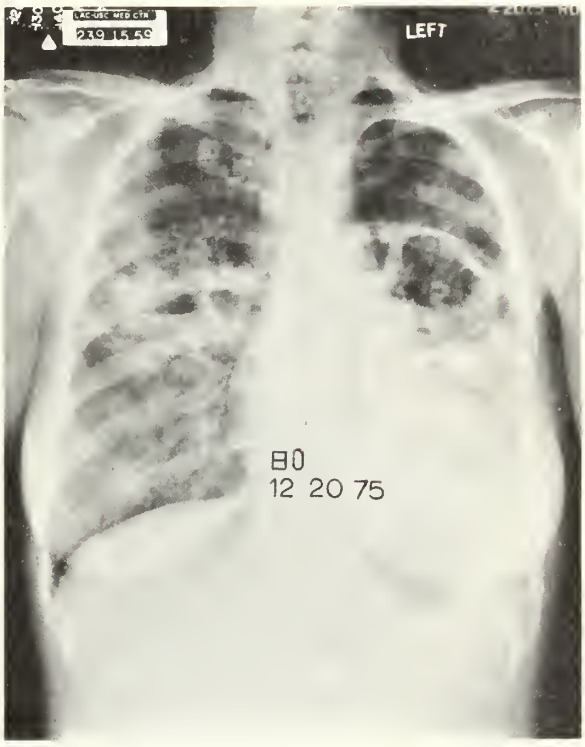

Figure 2.—Posteroanterior chest roentgenogram showing diffuse interstitial infiltration with multiple cavities in both lungs, two with air-fluid levels.

High doses of penicillin G, gentamycin, methacillin and chloramphenicol in varying combinations were given. Two bronchoscopic examinations, one with transbronchial forceps biopsy, were not rewarding. A bone marrow biopsy and aspirate did not identify an etiologic agent. A percutaneous trephine lung biopsy was carried out and showed only interstitial fibrosis and a histiocytic reaction in the alveolar walls. The patient died after a two-month stay in the hospital.

At autopsy there were cavities in both upper lobes, measuring 4 by 8 cm. The cavities had thick, densely fibrotic, bland walls (Figure 3). There was no pus in these cavities. In surrounding areas there was bronchopnuemonia. Anterior mediastinal lymph nodes were enlarged. There was no pleural fluid in either hemithorax. Nothing remarkable was noted on examination of the heart. Examination of the abdomen showed many large mesenteric and periaortic nodes. Cultures of the autopsy material did not grow any bacteria or fungi.

Microscopic examination showed many noncaseating granulomas with giant cells in the lungs (Figure 4), anterior mediastinal nodes, liver (Figure 5) and abdominal lymph nodes. Most of the granulomas were densely hyalinized, indicating long-standing advanced disease. Special stains for acid-fast bacilli and fungi were negative. Examination of the specimens under polarized light did not show birefringent particles. These features were consistent with a diagnosis of sarcoidosis.

Comment

The lungs are affected in more than 90 percent of the patients with sarcoidosis. Common pulmonary manifestations include bilateral hilar node enlargement with or without interstitial infiltration and fibrosis. Bullae formation may occur in some patients with extensive fibrosis. Uncommon pulmonary manifestations are pleural effusion, nodular shadows, calcification of the hilar nodes, pneumothorax, unilateral hilar adenopathy and localized lung infiltrate.[1] Pulmonary cavitation is rare in sarcoidosis. A major pulmonary radiology text does not include sarcoidosis in an exhaustive differential diagnosis of lung cavities.[2]

There have been a few reports of pulmonary cavitation in sarcoidosis.[3-5,8-11] Some of the reports leave open to question whether or not

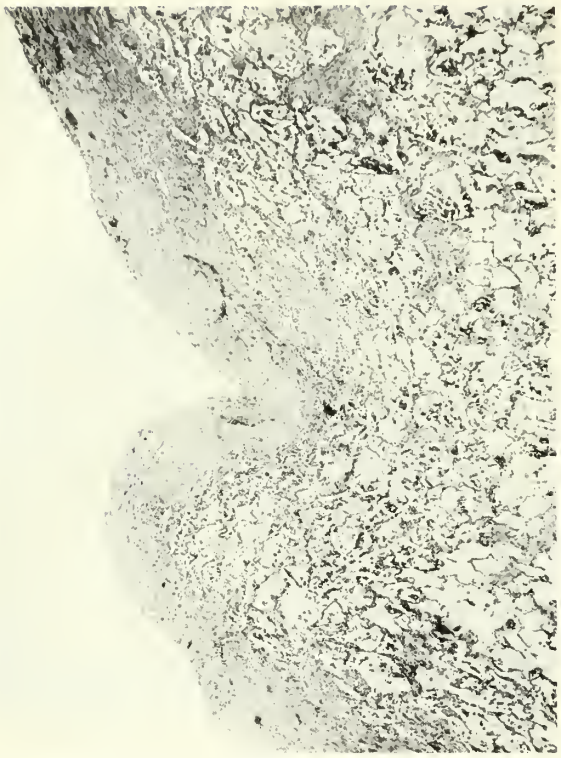

Figure 3.—Microscopic section of a cavity wall showing a thick, fibrotic wall with little inflammatory reaction (H & E × 75).

Figure 4.—Microscopic section of the lung showing noncaseating granuloma with giant cell. Surrounded by relatively normal alveolar wall (H & E × 200).

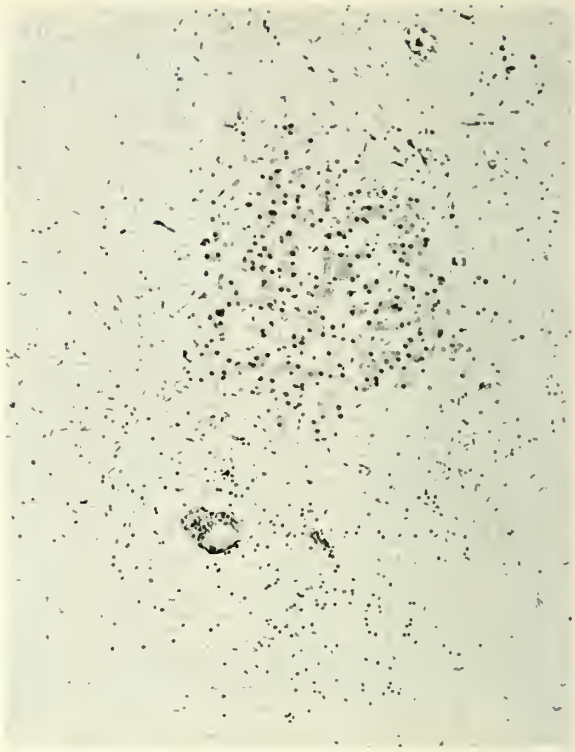

Figure 5.—Microscopic section of the liver showing relatively normal liver surrounded by hyalinized granulomatous tissue with giant cell (H & E × 120).

sarcoidosis was the primary cause of the cavitation. Hamilton and co-workers[5] emphasize that other causative agents must be excluded, such as fungi, mycobacteria or pyogens. Initially in our patient a pyogenic abscess was the likely diagnosis. However, failure to isolate an aerobic organism associated with lung abscess, failure to halt the progress of the illness with antibiotics active against anaerobes and aerobes, and the autopsy findings of thick-walled, bland, fibrous cavities seemed to exclude the diagnosis of bacterial abscess. Tuberculosis, fungal diseases and parasitic diseases were also excluded. There was no clinical or pathologic evidence to support Wegener granulomatosis or rheumatoid lung disease. Absence of a relevant occupational and clinical history ruled out the possibility of pneumoconioses, cystic fibrosis, bronchiectasis or traumatic cavities.

A review of the literature has found nine other cases of pulmonary sarcoidosis and cavity formation. This brings the total number of patients with cavity sarcoidosis to ten (Table 1). Seven of the nine patients in whom the clinical data were known were between 20 and 40 years in age. There were five women and four men. In half

of the cases there were emphysematous bullae or subpleural blebs and true cavities were not present. Therefore in only five patients, including the one reported here, were true pulmonary cavitations present. Our patient is the only case reported with true cavities in both lungs. Only the left lung was involved in three others and the fifth patient had right upper lobe involvement. The clinical manifestations included spontaneous pneumothorax in two patients, whereas, hemoptysis occurred in one patient and dyspnea in another; one patient with a cavity was asymptomatic. Although no consistent clinical features of cavitary pulmonary sarcoidosis emerged from the study, we feel that sarcoidosis should be considered in a patient with cavitary lung disease. Whether the institution of aggressive corticosteroid therapy would have changed the cause of the disease in our patient remains uncertain. The cause of cavity formation in sarcoidosis also remains unknown. Scadding[7] states that thick-walled cavities may form in one of three ways: (1) emphysematous bullae whose walls are thickened by secondary infection, (2) intercurrent pyogenic lung abscess and (3) necrosis at the centers of dense hyaline fibrosis formed by the coalescence of hyalinizing granulomas. It is our feeling that only the last category represents true sarcoidosis cavities.

Summary

A case of progressive cavitary lung disease is reported. The patient was found to have sarcoidosis. Other causes for cavitation were excluded. Sarcoidosis must be considered in a patient with cavitary lung disease, particularly in patients in those groups commonly affected by sarcoidosis: women, blacks and patients between 20 and 40 years old.

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TABLE 1—*Cases of Pulmonary Sarcoidosis and Cavity Formation*

Author	*Age*	*Sex*	*Race*	*Location*	*Size of Cavities*	*Course*	*Hilar Adenopathy*
Hamilton[5] ...	30	M	black	LUL cavity*	3 cm	Hemoptysis, stable course after surgical operation	yes
Harden[4]	31	F	black	Bilateral* midlung zone bullae, thick-walled cavity Left lung	4 cm	Cor pulmonale, died	no
	30	F	black	Bilateral upper lobe blebs, thick-walled cavity RUL*	4-5 cm	Spontaneous pneumothorax, underwent pleurectomy, thereafter chronically dyspneic on exertion	no
	41	M	black	Bilateral lower lobe and upper lobe emphysematous bullae	>6 cm	Underwent resection of LLL bullae, chronically dyspneic on exertion	no
Tice[8]	48	F	NA	RUL blebs	2 cm	Shortness of breath, cor pulmonale, died	yes
Hogan[9]	36	M	black	Bilateral apical bullae	>6 cm	Dyspneic, died	yes
Ustvedt[10] ...	39	F	white	Bilateral large apical bullae	>6 cm	Sudden severe hemoptysis, died	no
King[11]	NA	NA	NA	Bilateral apical bullae	>6 cm	Pleuritic chest pain, died	no
Bistrong[3] ...	20	M	white	LUL cavity*	<3 cm	Asymptomatic	no
Schiffner	31	F	black	Bilateral* upper lobe cavities	8 cm	Spontaneous pneumothorax, febrile course, respiratory failure, died	no

NA = information not available LUL = left upper lobe RUL = right upper lobe LLL = left lower lobe

*In these patients true cavities seem present.

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Force and Counterforce

To the Editor: My sincere thanks for the splendid "fourth leader" on "Force and Counterforce," which appeared in the August issue. I have seldom read a better medical editorial, and indeed I use the term "fourth leader" as the elegant style reminded me of the Swiftian leaders which used to appear in the London *Times*. When I was a younger man, we used to look forward to these every week when the Sunday paper arrived.

I agree with you wholeheartedly that this is not the time to dismount Dresden bulls, as both the shop and its contents must be preserved.

I well recall the manner in which "they" in the United Kingdom introduced the National Health Service Bill—a Conservative measure and one of Churchill's pets. The profession of medicine was neatly divided into the very old, to whom pensions were guaranteed, and the very young, to whom a reasonable early income was offered. After having gotten out these two rather forceful segments of the medical profession it was quite easy for Bevan to drive his "coach and four" through the rest of a disjointed profession. If only we would learn from previous experience, and wouldn't have to repeat the same mistakes.

Again my thanks, combined with congratulations, on your exposition of Swift's famous epitaph "saeva indignatio."

WALTER J. TREANOR, MD
Reno

An Alternative to Home Monitoring in Hypertension

To the Editor: When measuring blood pressure we have become more and more aware of an element of uncertainty. As Page[1] has recently stated, the technique had been so well established and is so simple that, for many years, results had been rarely suspected of being inaccurate.

Some of the errors in management of hypertension can no doubt be avoided by a program of home measurement especially when the four points advanced by Unger[2] are observed. Still, it may be argued that home reading of blood pressure is too invasive; as a morbid intrusion it tends to distort home life.

This, therefore, is to report a third alternative which I have found most satisfactory in identifying hypertensive patients, as well as in management:

Patients are advised to have their blood pressure checked by an office nurse on two or three occasions *between* consultations. In order to avoid factors of anxiety and of anticipatory suspense, it is proposed to adopt the following four provisos dictated by common sense as well as by experience.

1. Patients make the trip not as a special visit to the physician's office but combine it casually with shopping or other errands—and without an appointment.
2. Avoiding the waiting room with its conditioning atmosphere, they knock at the exit door, are speedily admitted and leave expeditiously.
3. The thought of adding to the bill might affect the blood pressure. In order to get this service free, patients have agreed not to ask a single question about the result and not to expect comments during the drop-in visit. Thus, expectative buildup of blood pressure will be minimal. They have been forewarned that, should they violate this stipulation, a fee for the service will be charged.
4. Patients drop in preferably in the morning hours.

I have used this drop-in method for more than 25 years and rarely feel the need for home monitoring. At times there have been substantial differentials between the consultation pressures and the lower "drop-in" pressures.

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Of Homes, Hospitals and Cocktail Lounges

A wonderful, spanking-new idea has been born: "Have your baby the natural way, in the warm and friendly atmosphere of your home, safe in the bosom of your family." It sounds great, and now and again a patient asks to go that route.

Is home-birth really so safe and so wonderful? A recent survey done by the Hawaiian Department of Health indicated that being born outside the hospital may pose a three-fold higher risk to the newborn. Neonatal mortality in home births was 29.9 per thousand as compared with 9.6 per thousand in the hospital setting.

At a recent convention of the American College of Nurse Midwives, press releases extolled the virtues of home delivery and urged parents to "actively participate in the miracle of their children's birth."

Some of us have been around long enough to know that this idea of home delivery is by no means new. We still have vivid memories of wearisome and worrisome deliveries, when at times the atmosphere was anything but friendly. We would try to keep the fretful expectant father busy boiling water, swatting flies, and finding newspapers to spread on the bed and on the floor. But this didn't always keep him from pacing back and forth, wringing his hands, and pleading "Can't you do something, Doc?" Some of us can even recall threats of bodily harm if anything went wrong.

Then we had the so-called "maternity homes." These were a step up. There we had a little more cleanliness, and the added safety afforded by a watchful "house mother," who could be with the patient throughout her labor. The care was pretty primitive by our present standards, and the perinatal morbidity and mortality still uncomfortably high. Small wonder, then, that the medical professions began pushing for hospital deliveries for everyone. Third party payors helped the cause. And the outcry for the relief of pain and suffering for women in childbirth made hospital delivery almost mandatory.

In the hospital the husband and family were not allowed in the delivery suite. The need for a "sterile field" was given as the reason, but we know in our hearts it was mainly because of an increasing fear of malpractice suits. Moreover, we physicians had the feeling of uneasiness having husbands peering over our shoulder as we struggled valiantly to bring the baby down over his wife's bloody perineum. So we barred the husband from the delivery room, labeling such observation as a form of voyeurism.

Quite naturally, there was a consumerist reaction. Hospitals were pictured as unhappy, unfriendly places, hospital personnel as heartless. Norman Cousins, writing in the *Saturday Review,* complained "There is something about the sterile and busy-busy routine of a hospital that depresses the spirit. Hospitals exude a kind of friendly unfriendliness."

Our French colleague Leboyer probably did more than anyone else to label our hospitals as too cold and impersonal, at least in the maternity wing. He espoused a return to "naturalness." A rebirth of Grantly Dick-Read's "natural childbirth" with an added touch of showmanship.

So again the pendulum swings. Now our hospitals are welcoming husbands and Lamaze "coaches" back into the birthing area. Daddy is even allowed to hold his newborn baby. Colorful paper adorns the walls, and soft music is piped in. Some hospitals are even installing "birth rooms" where the family can "actively participate in the miracle of birth." Much of this is good and can be accepted in the name of progress. But let's not go overboard. Hospitals are not hotels. There will continue to be a need for good clinical judgment to safeguard quality of patient care.

Cousins ended his article with a tongue-in-cheek remark:

> Hospitals—while we are on the subject—could perhaps provide better facilities for visitors. A colleague recently proposed that all hospitals be equipped with a cocktail lounge—"because most of the time you visit a hospital when somebody is either coming or going. In either case, a civilized place to wait would not be unwelcome."

Facetious, of course. But the point is made, and hospitals are responding. Let us all hope that in our eagerness to create a warm and friendly atmosphere we don't completely discard the stern principles and the strict disciplines that made our hospitals a safe haven for medical and surgical patients, as well as for mothers in labor.

E. R. W. FOX, MD
Coeur d'Alene, Idaho

A 'Good Gray Ship of the Line'

To the Editor: The following represents my personal views and, I feel, also reflects the feelings of many other physicians I have spoken with.

There is a responsibility to present a perspective, to gain a sense of balance in the recent publicity about medical care at the Naval Regional Medical Center (NRMC), or Oak Knoll Navy Hospital, in Oakland, California. On the surface it would appear to be a local or military matter, but there are other implications deep down, concerning the nature and future of medical care, physician training and public trust, and the proper role of mass media.

I feel in a way that I am writing an obituary, or perhaps a eulogy, to a lady—a proud lady, a "good gray ship of the line," one that has served long and served well. Oak Knoll Hospital started back in World War II as a group of low white wooden barracks on a former golf course in the Oakland foothills. At times, more than 6,000 patients, wounded from the Pacific campaigns, were under care at the same time. The Naval Prosthetics Research Laboratory became world famous for its work with artificial limbs and rehabilitation of amputees. Doctors used to make rounds on bicycles from building to building, and many a footrace with death was run during a nighttime emergency.

In 1968 the present building was opened, complete with a sophisticated clinical research center operated jointly with the University of California. During the Vietnam War the hospital was busy 24 hours a day, with surgery operating around the clock. Extra staff worked 36 to 40 hours straight to take care of the overload of acute cases, besides the regular care of persons on active duty, dependents and retired military personnel. Congressmen received letter after letter praising the staff of the hospital for their work and their results. Morale was high—the young staff fulfilling their primary goal of good medical care and happy to be stationed in the San Francisco Bay area.

After the war, as happens after every war, the budget and the staff were cut, and the "doctor draft" ended. But the patient load and the training responsibilities remained the same. The medical budget comes from the military budget, and if it comes down to repairing an aircraft carrier or buying new x-ray equipment, the line needs come first—these are the facts of military administration budgets and priorities. (Transferring extra funds and extra staff means taking from someone else's budget and manpower.)

Patients kept coming in, got better, were well treated and went home. More than two million people have been seen at the Center—their "silent" routine care taken for granted, unmentioned and unnoticed. At the same time, hundreds of doctors, nurses, corpsmen and technicians have been trained at the NRMC. The Center is a graduate training hospital, with a full range of services; interns, residents, medical students, and corpsmen pass through its halls for training, the same as at other medical centers such as Stanford, University of California, San Francisco, and San Francisco General Hospital, with whom it shares instructors, residents and medical students. The latest medical information is thus freely exchanged for the immediate benefit of the patients.

What then of the deaths so recently publicized? How could they happen in such a high quality hospital with dedicated medical personnel? What are the reasons, the motives, the implications in these cases?

It is ironic that the initial case, the death of a "routine gall bladder surgery patient," was of an acutely ill man who had an emergency surgical operation for an infected gall bladder and had associated medical disease, and died in septic or infectious shock. His death was discussed and reviewed, presented at the regular mortality and morbidity conference—*all* hospitals have these conferences where severe complications and deaths are discussed openly and critically by the hospital staff, to see what more could have been done, what shouldn't have been done, what can be learned for the future, how we can do a better job in a grim struggle with deadly disease *and* how we can eliminate human error. *All* large hospitals have two or three preventable deaths each year, due to human error. In training centers and in private hospitals errors will be made. Whether due to fatigue, inattention, false assumptions, overconfidence or ignorance, the very best medical centers have these tragedies. Every doctor has seen these things, and has that unspoken fear deep within that it will happen to him—it may already have occurred during his training or in practice, and it leaves an invisible but indelible scar on his conscience. To publish these events,

to hang this agony out in front of the public eye, would threaten to destroy physician training, patient-physician trust and the practice of medicine. It is a matter between the physician and the family of the patient, and to assume the public can be served by a glaring searchlight of media coverage is to assume that the errors were deliberate, or that more money or more machines or more people will eliminate these tragedies—or that punishment and fear will "make people more careful." It doesn't work that way.

What of the officer who began the investigation and raised the charges of poor patient care? His medical school education was paid for by the Navy with a signed contract for a career of eight to ten years in Navy medicine. After a Navy internship, he was offered his choice of an orthopedic surgery residency after a year's shipboard duty as a general medical officer. He refused this and chose anesthesiology, where he is an able, intelligent and very accomplished resident (he once saved the life of an unborn child by performing an emergency cesarean section in the middle of the night, at an affiliated hospital, while in training in obstetrical anesthesia—mother and child are doing well). After finishing the required two years of training and not wishing to take the optional third-year conditions, he rejected his next duty assignment, got a lawyer who works on military cases, lined up a job in civilian life and began a campaign to get out of his remaining four years of service—if possible by October when his new job was to begin. It is a complex situation, with promises made or implied but not kept, on both sides. Matters of integrity, honor, obligation and reciprocity are involved, and the outcome is as yet cloudy.

What of the role of the media in all of this? Were they duped, used, manipulated, suckered, drawn in over their heads by a situation larger than their ability to comprehend? Perhaps a better background into the nature of medical care, medical training and life-and-death in a hospital setting would have helped. Perhaps not. I know many fine physicians in the San Francisco Bay area who were at the NRMC at some time in their careers, who silently cringe at each new report, and who are angry and bitter at the many distorted and incomplete details. And what of the million, now healthy patients who have been treated well at the NRMC as one of their benefits for military service?

In future years a budget decision may force the closure of either Letterman Army Medical Center [the Army hospital in San Francisco] or the Naval hospital due to the cost of "earthquake-proofing" and building new outpatient facilities for both hospitals, when in fact either hospital could handle *all* the military medical needs of the Bay Area alone, if strengthened and staffed fully. Having served in the Navy, at the NRMC from 1970 to 1975, I have good friends and fond memories there. I enjoyed my service in the Navy, as I enjoy my private practice now. I would vote of course to keep the NRMC fully alive and well and functioning—politics and perverse publicity might say otherwise.

RICHARD E. TIRRELL, MD
San Pablo, California

Correction: Adenocarcinoma in the Small Bowel

IN THE SEPTEMBER ISSUE on page 251 the title of the communication from David A. Mulkey, MD, was incorrectly printed as "Adenoma in the Small Bowel." It should have read "Adenocarcinoma in the Small Bowel." The error was repeated in the text of the letter.

Refer to: Swanberg RG: The medical challenge of coping with stress (Medical Education). West J Med 127:354-356, Oct 1977

The Medical Challenge of Coping With Stress

RICHARD G. SWANBERG, MD, *Santa Rosa, California*

GRADUATION FROM medical school—what a terrific feeling. For each of us it is the time to celebrate the completion of a difficult step in personal growth. To achieve this step we have had to spend many years working very hard. Today our school pays homage to this diligence. Our medical degree is an honor, and we are very proud.

During our four years we have acquired a tremendous amount of knowledge about the diagnosis, pathophysiology and treatment of many diseases. Also, we realize there is a lot more to learn. Many challenges face us. Today I would like to focus on one of these: the medical challenge of coping with stress.

What is stress? Dr. Hans Selye, a noted physician who has spent his career in stress research, defines stress as "the nonspecific response of the body to any demand made upon it."[1] But most of us associate the word stress with high levels of nervous tension, frustration and anxiety, and psychological hang-ups. Many people today are on an emotional starvation diet—a shortage of love, understanding and involvement. The reasons for these stresses are legion: taxes, unemployment, illness and now, for us in California, the drought. Dr. Norman Q. Brill reminds us that the improved quality of life over the past 25 years, resulting from impressive advances in technology and medical care, seems to have been accompanied by disturbed interpersonal relationships, more anxiety about employment and security, greatly increased divorce and crime rates, and increased human unhappiness.[2]

Stress is so democratic—everyone has it. Everyone is becoming aware of it. In her best-selling book, *Passages,* Gail Sheehy describes people of all ages who have been frustrated, stifled and deflated by life's tensions.[3] Many of these people have withdrawn into a shell of isolation and hidden their true feelings to prevent themselves from further disappointment and rejection.

Several recent medical studies have shown that stress induced diseases have reached epidemic proportions. Heart attacks, ulcers, high blood pressure and skin disorders have all been traced to situations causing anxiety.[4] The medical profession, of course, is not immune to stress. Many of the personality traits that characterize a good physician—careful control of emotional expression, compulsive attention to details, conscientiousness and prolonged deferral of gratification—are traits that predispose some physicians to episodes of extreme depression. These doctors are much more likely to become divorced, become addicted to narcotics or commit suicide than the population as a whole.[5]

On a more personal note, the past four years have been filled with stressful situations. Getting into medical school, for example; who can forget anxiously waiting for that all-important acceptance letter to arrive in the mail. The oral and written exams were numerous. We were required to know a seemingly endless number of facts, many of which appeared to have little relevance to our long-term goal of becoming quality doctors. Many of us were also plagued by financial worries. We encountered multiple anxieties in the transformation from insecure students to young knowledgeable physicians. We can all remember dealing with hostile patients who did not want

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From an address delivered as a graduating medical student at the 23rd Annual Hippocratic Oath Ceremony, University of California, Los Angeles, June 3, 1977.

Reprint requests to: Richard G. Swanberg, MD, Community Hospital of Sonoma County, 3325 Chanate Road, Santa Rosa, CA 95402.

to talk to just a medical student. Missing our first spinal tap, intubating the esophagus instead of the trachea, flubbing the latest medical "pimp" question on ward rounds, and being on call and unable to get any sleep at night were all part of our tension-filled medical school experience.

Along with academic problems, many of us experienced emotionally difficult times. One of my classmates who became divorced while in medical school feels that although his marriage was not ideal to start with, the strains of medical school were enough to bring his marriage to an end. Several other classmates had tragic deaths occur in their immediate families. While these students were given academic help during their periods of distress, they were offered little emotional support from the school. All of these students mentioned that they would have gladly accepted counseling and advice if it had been offered. Perhaps this is one area of medical education that can be improved for future medical students. A medical school should act as a role model in dealing with our stresses and should be able to teach us to deal with our patients' anxieties. Now we apprehensively await one of the most emotionally and physically stressful years of our lives—internship.

With these thoughts in mind, how are we, the medical graduates of 1977, best able to help ourselves and our patients react to the everyday tensions of life? To start with, we must realize that a minimal amount of stress is necessary to add spice to one's life. An element of stress is involved with growth and is essential for sound personal functioning. One could avoid stress by never doing anything, but few things in life are as bland as complete inactivity. Indeed, who would enjoy a life of no runs, no hits and, especially, no errors?

However, there will be occasions in which our patients will be overwhelmed with stress. But as in any aspect of medicine, before we can offer a cure we must make the appropriate diagnosis. We have learned the art of obtaining a thorough medical history, and we should put this to good use. We must look for any of the cardinal signs of stress such as recent weight change, sleeping and concentrating difficulties, depression, or increasing cigarette, drug or alcohol consumption. If such signs are present, we must make the diagnosis. At this point we should just give Valium®, right? No, it is not that simple. Instead we must become involved.

Involvement with our patients must be a process, a journey, a way of life. It is the accumulation of simple, concerned actions which allows physicians to develop a sense of awareness and to become alerted to patients' needs. We have been taught to look at the whole person and not just his disease. We have been strongly criticized if we ever referred to our patients as the pheochromocytoma in bed six or the GI bleeder at the end of the hall. Instead, we have been encouraged to treat our patients with dignity and compassion and to understand how the stress of illness affects the patient, his family, his work, and the people around him. Healing takes place out of knowing our patients. We have discovered the worth in knowing the whole person in the context of his family situation and the extreme value in providing comprehensive and continuous health care. It is very encouraging that more than three quarters of this year's graduates are entering the primary care specialties in which a physician is best able to treat the entire patient.

The release of stress and anxiety has much to do with the healing process. A physician should be paid not just for what he knows but also for the comfort and support he can give. His prescription for healing should include a combination of both head and heart. A cure without care is dehumanizing. Yes, care is an absolute prerequisite for a cure (a point impressed on me in a sermon, "With Care," by J. Little, Senior Pastor, Lafayette-Orinda United Presbyterian Church, May, 1977). Helping the patient overcome his fears and his feelings of helplessness can be as vital to recovery as wonder drugs are to curing a diseased organ. The doctor's ability to connect with his patients enables him to talk a patient through a crisis or provide crucial comfort and reassurance through the touch of his hands. A physician must have the capacity to relate to others in a consistent manner and have concern and compassion for his fellow human beings.

The concerned physician can be a catalyst in helping his patients learn ways to overcome tension. In our training we have learned the value of the coping quotient in determining a person's ability to handle stress. This is an index which evaluates stressful situations in someone's life and can act as a predictor of the chances of having a serious illness in the upcoming year. Those people with more skills, assets and resources, and with more versatile defenses, tend to do better under stressful situations. But for those who do

not cope as well, what can we do? We can offer solutions such as relaxation techniques. In his book *The Relaxation Response,* Dr. Herbert Benson extoles the virtues of relaxing and meditating to cope with tension.[6] Although meditating will not make your problems disappear, it can give you a different perspective. We can also encourage our patients and ourselves to have an optimistic and enthusiastic outlook on life. You should not underestimate the delight of simple pleasures, like rain or the price of coffee dropping 20 cents a pound. Even after the greatest personal defeats, the depressing thought of being a failure is best combated by taking stock of all your many past achievements. Such conscious stock-taking is most effective in reestablishing the personal self-confidence and motivation necessary for future success.[1] An optimistic frame of mind undoubtedly contributes to anybody's physical and emotional health.

All of us who graduate today have shown a great desire to learn and a strong sense of concern for the well-being of other people. We all expect to work hard meeting the challenges and frustrations in helping our patients solve their own problems. Sir William Osler challenged his fellow physicians to maintain coolness and presence of mind under all circumstances, calmness amid storm, clearness of judgment in moments of grave peril; in short, to remain imperturbable in any situation.[7] This is a difficult challenge, one that has caused many physicians much distress. Perhaps we, becoming physicians in 1977, should modify Osler's ideas to allow for greater releases of our emotional tension as a way of preventing ourselves from becoming overwhelmed with stress. In fact, this approach may be an important key to the medical challenge of coping with stress.

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The Towel Trick for Detecting Breast Carcinoma

DR. HODGKINSON: "The procedure consists of stretching a towel over the breast and palpating the breast in all directions directly over the towel, quickly sweeping the hand over the breast.

"The principle of the towel trick is probably somewhat the same as examining a breast with soaped hands . . . The towel trick has been found to be well adaptable to office practice for asymptomatic women and is a more fastidious technique than using soaped hands. I have experimented with various types of material, but I find that a freshly ironed, smooth hand towel, such as usually found in hospitals or offices, serves very satisfactorily.

"I have found the towel trick very valuable in detecting small breast masses that are difficult to feel otherwise. Often, the mass can first be located with a towel and then be detected easily by direct palpation. Although any type of smooth cloth material can be used for this examination, the hospital towel works very satisfactorily provided it is smooth and dry. I think that by incorporating this technique into the routine examination of breasts, it will be found of some value in detecting breast masses which are otherwise difficult to feel."

—C. PAUL HODGKINSON, MD, *Detroit*

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Special Article

Refer to: Computed tomography—The views of Blue Shield of California. West J Med 127:357-361, Oct 1977

Computed Tomography

The Views of Blue Shield of California

WITH ALMOST EXPLOSIVE FORCE, computed tomography (CT) has burst upon the health care system. Revolutionizing the science of diagnostic imagery, CT has been seen as the most startling development since Dr. Röntgen's initial discovery. Originally, CT was confined to intracranial studies, where the greatest amount of data have been acquired. Subsequently, instruments have been devised for scanning sagittal views of the body. Because of the expense of CT instruments ($400,000 to $600,000), the cost of operation and the proliferation of devices, immediate alarm concerning the impact on the economics of health care was expressed by private and government payors of medical expenses. In the attempt to contain the uninhibited utilization of this novel device, various government agencies and Blue Shield and Blue Cross plans announced that payment would be allowed only for CT brain scans, not for those of the body. Going even further, the Bureau of Health Insurance decreed that, for Medicare beneficiaries, payment could be allowed only when the EMI scanner was used.

Since Health Systems Agencies (HSA) in California, authorized by AB4001, were in the embryonic stage, they were not fully prepared to regulate the appropriate distribution of CT scanners in the state. Currently, the California Department of Health is conducting hearings to help develop guidelines for the issuance of certificate of need.

In an attempt to develop an equitable policy concerning utilization and reimbursement for CT, the Medical Policy Committee of Blue Shield of California, as a fiscal intermediary for Medicare, Medi-Cal (California's Medicaid program) and CHAMPUS and its own standard program, decided to create an ad hoc committee with a distinguished membership.* Three meetings were held by this ad hoc committee and its report was presented at a special meeting of the Medical Policy Committee on January 12, 1977. The following is a summary of the conclusions.

Discussions by Committee

Ralph Schaffarzick, MD, Senior Vice President and Medical Director of Blue Shield of California, opened the first meeting of the ad hoc committee to inform the members of their charge and provided an agenda designed to proceed from the scientific through and including economic factors. The charge of the committee was to develop guidelines for utilization and reimbursement of computed tomography. In addition, the committee developed certain guidelines for distribution of computed tomography, since this has a direct bearing on utilization.

At the onset, Dr. Schaffarzick and Thomas C. Paton, President of Blue Shield of California, described the problems that computed tomography has presented to the private sector and governmental agencies in regard to reimbursement

Adopted by the Blue Shield of California Medical Policy Committee, January 12, 1977, and approved by the Blue Shield of California Board of Trustees, February 16, 1977.

Reprint requests to: Ralph W. Schaffarzick, MD, Medical Director, Blue Shield of California, Blue Shield Plaza, 2 North Point, San Francisco, CA 94133.

*Roy Cohn, MD—Professor of Surgery at Stanford University School of Medicine; Gladden V. Elliott, MD—radiologist, CT scanning specialist and member of the California Medical Association's Council; John Gamble, MD—internist and regent of the American College of Physicians; Richard W. Gonzalez—Industrial Relations Manager, Ford Motor Company, and Member of the Medical Policy Committee of Blue Shield; Edgar G. LaVeque, MD—Chairman of the Committee, family practitioner, former member of the Blue Shield Board and past chairman of the Blue Shield Medical Policy Committee; Philipp M. Lippe, MD—neurosurgeon, Clinical Associate Professor of Neurological Surgery at Stanford University and president-elect of the California Association of Neurological Surgeons; Donald Macrae, MD—Professor of Neurology at the University of California, San Francisco; Frank Mainzer, MD—radiologist, CT scanning specialist and member of the radiology department of San Francisco's St. Francis Hospital; Gerald M. McDonnel, MD—radiologist, CT scanning specialist at the Hospital of the Good Samaritan in Los Angeles and member of the National Survey Committee of the American College of Radiology, and Ralph O. Wallerstein, MD—Internist/Oncologist and Governor of the American College of Physicians for Northern California and Nevada.

for diagnostic studies provided by CT scanning. Concerns over the major impact of this new technology were well known to the committee and throughout the discussion it became apparent that utilization of these new procedures has had a major impact on medical economics in general. Therefore, the validity of CT scanning in the medical armament of diagnostic radiology immediately became an issue before the committee. A statement as to the actual validity of CT scanning was proposed. After considerable discussion, a policy statement of the American College of Radiology, with modification, was adopted as follows:

Computed tomography is a proven radiologic modality, which provides valuable clinical information in the early detection, differentiation, and demarcation of diseases of the head and body.

Abundant documentation of its safety and diagnostic efficacy has been presented in the scientific literature.

It is particularly helpful in solving problems where there is conflicting information from other radiological or laboratory studies.

It frequently does replace other examinations, many of which carry greater risk, discomfort and expense.

Access of the public to computed tomography is essential.

During the meetings considerable discussion took place about areas of practice not directly included in the committee's charge.

First, there is no longer any question that both head and body CT scans are valuable techniques. Both have demonstrated efficacy in examination of the head and body. They are no longer experimental. Every effort should be made to communicate these facts to the appropriate agencies of government.

Second, CT scanning does have a positive as well as negative impact on the cost of medical care. The interrelationship between computed tomography and radionuclide scans, electroencephalography, pneumoencephalography, ventriculography, angiography, posterior fossa pantopaque myelography, diagnostic ultrasound and conventional contrast media result in reductions in the number of traditional tests carried out. There is also a positive impact on total hospital days, since CT does in certain cases replace procedures requiring hospital admission with an outpatient procedure. Unfortunately, no scientific data to evaluate this cost reduction are available and the committee would encourage such research to permit accurate evaluation of the macro-economic impact of computed tomography.

Third, the number of different imaging procedures, such as diagnostic radiology, angiography, ultrasound, nuclear scans and computed tomography imaging, make selection of appropriate studies for a specific case increasingly difficult. *Ideally a physician with expertise in imaging and in charge of all these modalities should consult with the clinician concerning which procedure is best suited in a specific clinical situation.*

Last, the committee believes the major thrust of Blue Shield of California and medicine itself should be in educating the medical profession to utilize CT scanning properly. One must constantly weigh the purpose for obtaining any diagnostic study, and it is probable that the present high rate of utilization of CT scanning will subside as the educational process takes place.

Physicians in their enthusiasm to perfect the depth and accuracy of their diagnosis must re-evaluate the relationship of advancing technical ability in regard to the final outcome of the disease in question. Every physician should apply medical and moral judgment to his decisions with respect to each patient.

Indications for CT Scanning

Head Scan

After review of literature and personal experience of the committee, it was concluded that CT *may be* necessary if the following are present:

A. Symptoms
   1. Headache of significant magnitude (Persistent symptoms after neurological evaluation)
   2. Vertigo
   3. Altered consciousness
   4. Seizures, excluding febrile
   5. Symptoms suggestive of transient ischemic attacks
   6. Dementia

B. Physical Findings
   1. Papilledema, or other signs of increased intracranial pressure
   2. Apraxia or aphasia
   3. Visual field defects
   4. Cerebellar dysfunction signs
   5. Hemiparesis
   6. Other focal neurological signs

C. Unresolved Medical Problems
   1. Vascular
      a. Cerebral infarction
      b. Subarachnoid hemorrhage
   2. Traumatic
      a. Hematoma, subdural or intracerebral hematoma
      b. Orbits
      c. Loss of consciousness or declining neurological status
   3. Neoplastic
      a. Primary brain tumor
      b. Intracranial metastases
   4. Congenital Lesions
      a. Hydrocephalus
      b. Encephaloceles
   5. Cerebral Deterioration
      a. Brain atrophy
      b. Acquired hydrocephalus
      c. Non-infectious, infiltrative disease
   6. Infections of central nervous system
   7. Abnormalities seen on skull x-ray, e.g., calcification

D. Serial studies for documentation of response to treatment
   1. Neoplasm, after surgery, radiation, and/or chemotherapy
   2. Hematoma, arterio-venous malformation
   3. Hydrocephalus, after shunt
   4. Management of brain abscess

It was the opinion of the committee that there were no medical contraindications to the application of a head scan; however, the medical necessity in each case should be judged in relation to the preceding criteria.

Body Scan

Neck. The neck is a difficult area to study. There are too many artifacts which cannot be separated and it was felt proper to deny claims for CT scanning of the neck.

Pleura. CT scanning is particularly useful in the identification of pleural nodules which may escape detection by conventional x-ray studies or radionuclide scans. This may prevent unnecessary thoracotomy for solitary lesions of the lung where metastatic seeding has already occurred in the pleura.

Pulmonary Emboli. There is no advantage to CT scanning in detecting pulmonary emboli. Radionuclide methods are superior.

Lung. All claims for CT scanning of the lung should be reviewed, since conventional x-ray studies and tomography provide excellent studies of the lung. It should be noted that slow scanners are incapable of providing sufficient resolution.

Heart. Claims for studies of the heart should be denied. Because of the rapidity of cardiac motion, CT scanners at present are incapable of studying the heart with any degree of accuracy. (Experimental studies in dogs have shown promise, however, in quantitating the magnitude of myocardial infarction.)

Aorta. Claims for studies of the aorta with CT scanning should be reviewed by a medical consultant. Although aortic arch studies using conventional angiographic methods are invasive, they still provide more accurate information.

Mediastinum. Claims for studies of the mediastinum should be accepted, as CT has been shown to be useful in defining the nature of superior and anterior mediastinal and paramediastinal lesions.

Spine and Spinal Cord. CT scanning for the investigation of syringomyelia is acceptable. All other claims for CT scanning of the spinal cord should be reviewed. Currently, technetium bone scans or myelograms are better procedures for imaging the spine.

Retroperitoneum. CT scanning of this area should be accepted when the suspected diagnosis is an adrenal tumor or retroperitoneal tumor or mass.

Pancreas. Accept CT scanning for pancreatic tumor or pseudocysts; though the discussion by the group did point out B-mode ultrasonic scanning in this area and the other retroperitoneal spaces should be considered effective. Utilization of CT scanning for this area should not be denied.

Liver. Accept claims for studies of the liver. CT scanning and nuclear scanning are complementary to each other. The choice of nuclear scanning or CT scanning must be determined in each individual case.

Kidney. A CT scan should not be the primary modality for kidney study. It should be preceded by an intravenous pyelogram, ultrasonic study, or possibly cyst puncture.

Gallbladder. Studies of the gallbladder and biliary tree seem to be sufficiently accurate to accept

a CT scan of this area in the presence of suspected obstructive jaundice. It would incidentally include the liver and pancreas in the same area.

Abdominal Aorta. Claims for CT scans should be reviewed because ultrasound scanning is easier, less expensive and just as accurate.

Uterus, Ovary, Bladder and Prostate. In this area, CT scanning should be used primarily for staging of tumors and extension of disease; however, it also may be useful in other disease processes in the pelvis, for example, abscesses and cysts.

Extremities. There is no justification at present for the use of CT scanning of the extremities.

Treatment Planning

CT scanning may be necessary for planning radiation therapy of certain tumor masses.

Blue Shield of California believes the previous sections reflect the latest available information on computed tomography. It is realized this level of understanding will change and periodic review of this statement is indicated.

Fees

Various technical articles on cost factors in computed tomography as well as data from claims were considered in recommending the level of payment by Blue Shield of California. The following general principles were adopted:

- The economic life expectancy of current CT models is approximately five years.
- The professional time requirement of each scan varies between 15 minutes and an hour.
- The use of contrast media adds a recognizable cost and risk factor to the procedure.
- Costs in California will be higher than in most other areas of the United States due to higher real estate values, the labor market and the like.
- Costs are based on 2,500 head scans or 1,500 body scans per year if the machine is fully dedicated to specific utilization of specific function.

Appropriate Allocation of CT Scanners

In developing this statement, emergency regulations on computed tomography scanner distribution filed on December 7, 1976, by the Director of the California Department of Health; policy statements on CT scanner distribution by the Board of Directors of the California Association of Neurological Surgeons and the American Academy of Neurology; and procedures being employed in other states to administer certificate of need legislation were reviewed.

No single set of criteria was found to meet the dual requirements of medical need and economic justification. The availability of a CT scanner for emergency diagnostic evaluation of head trauma may require placing scanners in localities where overall utilization will not support the economics of CT scanning. The existence of large regional medical centers may produce numerical relationships between CT scanners and need indicators substantially in excess of established community criteria. This may not indicate excessive utilization if the center in fact provides care well beyond the boundaries of the local community.

It was concluded that economic justification for a CT scanner requires a demand level equivalent to 2,500 annual head scans or 1,500 annual body scans on a fully dedicated unit. The benchmarks that would indicate an appropriate level of demand are:

- An unserved population area of 150,000 for head scans or 300,000 for body scans.
- A hospital with 250 acute care beds unserved by a CT scanner.
- A hospital currently properly utilizing 30,000 general radiography imaging procedures per year.

The following subjective criteria are needed to insure proper utilization of a CT scanner:

- Existence of an adequately trained imaging physician and a well rounded radiographic service.
- Existence of an active neurological or neurosurgical service, or both, involved in the care of intracranial problems available to the facility for support of a head scanner.
- Existence of active medical and surgical services sufficient to treat conditions diagnosed through computed tomography body scans.
- Available technical staffing sufficient to service the unit.

Determination of need should be made at the most local level and exceptions granted with appropriate justification. Each unit should be placed to recognize the geographic as well as the demographic characteristics of the area served as well as the distribution and practice patterns of spe-

cialties utilizing CT scanning. In all instances, CT scanners should be placed in a locality subject to adequate peer review. Location of a unit in an individual physician's office should meet the same distributional criteria as those located in a hospital. The instances where a unit is located other than in or contiguous to a general hospital should be rare because of the interrelationship between CT scanning and other medical services.

Summary

The Blue Shield of California ad hoc committee concluded:

- Computed tomography is a proven radiologic modality, which provides valuable clinical information in the early detection, differentiation, and demarcation of diseases of the head and body.

Abundant documentation of its safety and diagnostic efficacy has been presented in the scientific literature.

It is particularly helpful in solving problems where there is conflicting information from other radiological or laboratory studies.

It frequently does replace other examinations, many of which carry greater risk, discomfort and expense.

Access of the public to computed tomography is essential.

- Both head and body CT scans are valuable, established techniques, no longer experimental.
- CT scanning has a positive and negative impact on the cost of health care.
- Ideally, a physician with expertise in imaging and in charge of all these modalities should consult with the clinician concerning which procedure is best suited in a specific clinical situation.
- Physicians in their enthusiasm to perfect the depth and accuracy of their diagnosis must reevaluate the relationship of advancing technical ability in regard to the final outcome of the disease in question. Every physician should apply medical and moral judgment to his decisions with respect to each patient.
- Conditions where CT scanning may be indicated are delineated.
- In the determination of the recommendation for the level of payment by Blue Shield of California, certain general principles were adopted.
- Benchmarks to assist in the determination of appropriate allocation of CT scanners were developed.
- This report has been transmitted to the California Department of Health and the Bureau of Health Insurance.

Refer to: Babb RR: Intestinal gas (Medical Information). West J Med 127:362-363, Oct 1977

Medical Information

Intestinal Gas

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LEVITT AND COLLEAGUES, in a series of illuminating articles published over the past five years, have elucidated the source and composition of intestinal gas, and examined its role in the production of abdominal pain.[1-6] Since "too much gas" is an exceedingly common and frustrating complaint, this brief review has been written to further publicize the results of their studies.

Volume of Intestinal Gas

At any given time, one's small intestine contains 30 to 200 cc of gas.[1,2] The amount of flatus passed per hour is usually less than 100 cc, and over 24 hours averages 400 to 1,200 cc.[1,2] Seven control patients noted the passage of flatus 13.6 ± 5.6 times per day.[3]

Many patients with complaints of excessive gas probably have normal volumes of flatus.[4] Occasionally, however, malabsorption of certain carbohydrates, as in lactase deficiency, may lead to an increased volume of intestinal gas. One such patient excreted four to five times the normal amount of flatus and passed gas 34 times per day.[3] The symptoms were greatly improved by ingestion of a lactose free diet.

Source and Composition

Using an argon washout technique, Levitt and co-workers have determined the nature of intestinal gas.[1,2] Argon is infused into the upper small intestine, and subsequently gas is collected from the rectum and analyzed. The five major components of flatus are nitrogen (23 to 80 percent), oxygen (0.1 to 2.3 percent); hydrogen (.06 to 47 percent), methane (0 to 26 percent) and carbon dioxide (5.1 to 29 percent). Since the latter three are not found in air, they must be produced within the gut.

Hydrogen (H_2) is normally produced by bacteria in the colon acting on dietary, nonabsorbable substrates, such as carbohydrates and beans.[1,2] Certain bacteria may catabolize as well as manufacture H_2, and the final concentration in flatus represents the outcome of these two processes. In one experiment, the giving of neomycin to rats increased H_2 production, presumably by inhibiting those bacteria responsible for catabolism of H_2.[5]

Methane (CH_4) is likewise produced by bacteria within the colon. Approximately a third of adults harbor such a flora, and two thirds do not.[1] Reasons for this difference are not clear. The amount of methane in the stool is largely responsible for whether or not the stool "floats," rather than the amount of fat contained.[6] Therefore, floating stools are not necessarily indicative of steatorrhea.

Carbon dioxide (CO_2) comes from two sources. Large amounts are released when gastric acid is neutralized by bicarbonate, but most of this is absorbed in the small bowel. A second source is fermentation reactions, as with H_2, in the colon.[1,2]

Nitrogen (N_2) probably comes from both swallowed air and blood. Production of H_2, CH_4, and CO_2 in the colon lowers the partial pressure of N_2 in the colonic lumen to below that of blood leading to diffusion from blood into the lumen.[1,2]

Finally, as noted above, the oxygen (O_2) content of flatus is quite low due to O_2 utilization by colonic bacteria.[1,2]

Gas and Abdominal Pain

Using the argon infusion technique, Levitt[4] and associates found 18 patients complaining of excessive gas and abdominal pain to have similar volumes and composition of intestinal gas as measured in ten control subjects. In contrast, however, such patients complained of increased abdominal pain when the argon was being infused, and showed a significantly delayed transit of the gas from small intestine to rectum. Such results suggest "too much gas" may be secondary to disordered motility, and not increased amounts of gas per se.

Conclusions

- Of the five gases found in flatus (N_2, O_2, H_2, CH_4 and CO_2), three are produced mainly in the colon (H_2, CH_4 and CO_2), and cannot be accounted for by swallowed air.
- Colonic bacteria are very important in determining the composition of intestinal gas in that they utilize O_2 and perhaps H_2, produce

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H_2, CH_4 and CO_2, and by these actions allow for the diffusion of N_2 from blood into the colonic lumen.

- Although attention to excessive air swallowing and change in diet may help some patients with "too much gas," alteration of abnormal gut motility may be of greater therapeutic benefit.

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Refer to: Cohen JR: Pathogenesis of hemolysis in immune hemolytic anemia (Medical Information). West J Med 127: 363-365, Oct 1977

Pathogenesis of Hemolysis in Immune Hemolytic Anemia

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AUTOIMMUNE HEMOLYTIC ANEMIA is not an uncommon problem in clinical medicine, and when it occurs it can be quite perplexing to the practitioner. In recent years our understanding of the mechanisms involved in immune red cell destruction has advanced considerably. This discussion will attempt to summarize some of these mechanisms and relate them to clinical decisions concerning course and treatment.

Hemolysis due to immunologic mechanisms is caused by a reaction between antigenic sites on the surface of the red blood cell and circulating antibody, with or without the participation of complement. The basis for detecting the presence of such a reaction is the antiglobulin test, otherwise known as the Coombs' test.[1] Antiserum is produced by injecting rabbits with human immunoprotein, either antibody or complement. The animal makes antibody to whatever is injected. That antibody can be purified and then reacted *in vitro* with a patient's washed red blood cells (RBC). If the cells agglutinate, the test is positive. By serial dilutions the degree of positivity can be quantitated.

In a recent review,[2] Wendell Rosse has classified the Coombs' test results according to whether antibody alone is detected on the red cell, antibody plus complement, complement alone, or neither antibody nor complement. This classification is useful in understanding the pathophysiology of immune red cell destruction.

Antibody Alone on RBC

In 1967, LoBuglio and co-workers showed that red blood cells coated with IgG would bind to monocytes.[3] That this binding was inhibited by excess IgG, and more specifically by excess Fc fragments, suggested that there was a binding site on monocytes for the Fc fragment of IgG. Electronmicrography showed that the monocytes caused membrane injury to the red cells coated with IgG, causing them to become spherocytes. Spherocytes were subsequently sequestered in the spleen. In the absence of monocytes, IgG caused no membrane injury. Cells coated with IgM did not bind to monocytes.[4] Subsequent workers have shown that there are subclasses of IgG: IgG_1, IgG_2, IgG_3 and IgG_4. Monocyte receptors have been found only for subclasses IgG_1, and IgG_3.[5] IgG_2 and IgG_4 will not inhibit monocyte binding of cells coated with IgG_1 and IgG_3 but these two subtypes will inhibit each other, suggesting that there is only one binding site.[6] Radiolabeling studies have showed *in vivo* that cells coated by IgG are sequestered in the spleen.[7] The characteristic of autoimmune hemolytic anemia with a Coombs' test positive for antibody alone (the "gamma Coombs' "), therefore, is an IgG antibody, spherocytes and splenic sequestration.

Antibody Plus Complement on RBC

In 1968 Huber and co-workers[8] showed that there was a second monocyte receptor; this one for the third component of complement. That this receptor was separate from the above described

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IgG receptor was concluded from the inability of free IgG to inhibit the binding. Cells coated with C1, C1,4 and C1,4,2 did not bind, and the addition of C5,6,7 did not enhance the binding. It has been long known that IgM binds complement more readily than IgG.[9] This is felt to be due to the fact that complement fixation requires two Fc fragments a specific distance apart. A single molecule of IgM, which has five Fc fragments, can accomplish this, whereas two molecules of IgG must be adherent to the red blood cell at the correct distance apart to allow for the binding of C3.[10,11] Chromium[51] studies have shown that red cells coated with IgM and complement, unlike those coated with only IgG, tend to be sequestered in the liver preferentially, rather than the spleen. It has been shown both in experimental animals[12] and in man,[13] that some of these cells are subsequently released from the liver. This can be explained by looking at the fixation of C3 in somewhat greater detail. When adherent to a red cell, C1,4,2 is able to cleave C3 into subfragments. The fragment known as C3b adheres to the red blood cell, and the monocyte receptor is specific for C3b.[11] A serum enzyme, C3b inactivator, can cleave C3b leaving a second subfragment, C3d, adherent to the red cell. There is no monocyte receptor for C3d, hence the red cell is protected from sequestration and destruction.[14,15] This explains the seemingly paradoxical finding that autologous red cells from some patients with cold agglutinin disease survive longer when reinjected *in vivo* than infused matched donor cells.[16]

Complement Alone on RBC

Whereas IgM has been shown to readily fix complement, the IgM itself does not adhere well to the red cells at room temperature. The IgM may come off the red cell *in vivo,* as when it is fixed in a cool extremity and removed at core temperature, or it may be removed *in vitro* when the red cells are washed at 37°C. Therefore, most cases of "cold" hemolytic anemia are IgM mediated, but only complement is detected when the Coombs' test is done. Such Coombs' tests are reported as "nongamma." Whereas, as discussed above, these cells are subsequently sequestered in the liver, complement can itself cause intravascular hemolysis. This requires the completion of the complement sequence through C9, at which point the red cell lyses.[17,19]

No Antibody or Complement Detected

There are some patients who appear to have all the signs and symptoms of classic immune hemolysis but in whom results of a Coombs' test are negative. It has recently been shown by Gilliland and associates,[19-21] using a sensitive complement-fixing antibody consumption test, that such red blood cells do indeed have a small increase in the number of IgG molecules adherent to their red blood cells. Whereas normal red cells have approximately 35 molecules per red blood cell and commercial Coombs' antisera cannot detect less than 200 molecules, Gilliland has found hemolysis with as few as 70 molecules of IgG per red blood cell.

The treatment of immune hemolytic anemia depends both on the underlying cause and upon which of the above types of immunologic reactions is involved. Most drug or viral related hemolyses are self-limited once the offending agent is removed or infection over. Hemolysis related to lymphoma or connective tissue disease may improve with treatment of the disease. From the above discussion, it is evident that the treatment of an IgG idiopathic hemolytic anemia should include serious consideration of a splenectomy. This gives up to 68 percent response in some series, although some of these patients subsequently may require continuous steroid treatment.[22]

Splenectomy clearly is not indicated in the hemolyses involving complement, since most sequestration and red blood cell destruction is here occurring in the liver. Steroids are often of benefit. The mechanism of action of steroids in hemolysis is not known, although they have been shown to decrease cell bound IgG,[23] and increase free IgG, implying a decrease in red cell-antibody affinity. More important, steroids have been shown to decrease monocyte binding of IgG-coated red blood cells.[24] Steroids also are lympholytic and may work partly by decreasing antibody production. This should be a slow action, however, and the response to steroids is often fairly dramatic.[25] Although up to 80 to 90 percent of patients with autoimmune idiopathic hemolytic anemia may respond to therapy with steroids, in a number of these patients steroid administration will have to be maintained indefinitely. Although cytotoxic agents have been used with some success in patients refractory to steroids, these should not be employed unless hemolysis cannot be controlled by steroids and splenectomy.[26]

This has been a brief attempt to present one way to approach the evaluation of a patient with an immune hemolytic anemia. Although sorting out the finer details of IgG subclass or quantification of IgG molecules requires a sophisticated laboratory, an initial understanding of the pathophysiology and initial treatment decisions can be made based on the type of Coombs' reaction described above. This information is available in any hospital blood bank laboratory.

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Combating Insulin Overtreatment in Children

DR. ROSENBLOOM: "The problem that we see as the most common error in the management of diabetes in children . . . is overtreatment with insulin. We recommend reducing the insulin dose to the pre-overtreatment dose or to the usual dose of 0.6 to 0.7 units per kg of body weight per day. We try all-NPH (neutral protamine Hagedorn) or all-Lente® if a mix has been used for unclear reasons. There may be a several weeks' period of increased glucosuria and ketonuria following reduction. And hypoglycemic symptoms may actually increase or emerge for the first time, indicating the need for further and faster reduction in decrements of 10 to 20 percent at four- to ten-day intervals."

—ARLAN L. ROSENBLOOM, MD, *Gainesville, FL*

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BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

RECENT ADVANCES IN PLASTIC SURGERY—Number One—Edited by James Calnan, FRCP, FRCS, Professor of Plastic and Reconstructive Surgery, University of London, Royal Postgraduate Medical School and Hammersmith Hospital, London. Longman Inc., 19 West 44th Street, New York City (10036), 1976. 210 pages, $28.50.

The tenor of this book is set by the editor in his preface when he says that any technique or understanding of disease that benefits the patient is an advance, and that anything new in the past five years can be considered recent. Therefore, one should not expect anything startling or really new when reading the book. However, one may indeed arrive at a better understanding of some areas of plastic surgery.

The chapters on the rheumatoid hand are very worthwhile in view of an increasingly older population. The use of prosthetic joints and the extension of various tendon transplants in combination with joint reconstruction hold promise for many of these patients. Probably, the best chapter follows and is that relative to speech, particularly the nasal escape of air, written by the editor. The discussion of cleft palate repair and flap pharyngoplasty is only a postscript in an otherwise excellent presentation.

The discussion of automobile injuries holds nothing new and constitutes only a review. The same is true of the chapter devoted to a statistical survey of burn admissions.

There is a discussion of the organization of plastic surgical services in urban guerrilla warfare which is very interesting but includes nothing relative to advances in plastic surgery.

A handy pocket reference can be found in the chapter on chronically swollen legs. However, this topic is more thoroughly discussed in other books and papers. The same evaluation can be made of the material on conservative treatment of leg ulcers.

There is an excellent review on the planning and design of pedicle flaps along axial blood supply patterns. The use of free flaps is touched upon. However, these are still in the realm of laboratory research surgical procedures. Their wide use in clinical plastic surgery will depend upon the development of better and more easily used microsurgical techniques.

Finally, the last two chapters deal with cancer and its treatment by massive surgical resection and reconstruction and the use of radiation therapy. The methods and techniques discussed are those used in many medical centers in recent years.

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CONTROVERSY IN CARDIOLOGY—The Practical Clinical Approach—Edited by Edward K. Chung, MD, Professor of Medicine, Jefferson Medical College of Thomas Jefferson University, and Director of the Heart Station, Thomas Jefferson University Hospital, Philadelphia. Springer-Verlag New York Inc., 175 Fifth Avenue, New York City (10010), 1976. 299 pages, with 99 figures, $29.80.

The title of the book brings to mind the eminently successful volumes *Controversies in Medicine* edited by Ingelfinger and associates, and the popular sessions of the annual meetings of the American College of Cardiology "Controversies in Cardiology." In these, one author, or one speaker, respectively, presents a viewpoint and another an opposite viewpoint. In the above named book, one of the editors writes a comment after the presentations facilitating the reader's perception of the controversy. One would expect this book to follow the pattern, but it does not. The editor elected to ask *one* writer to present both sides of the controversy.

The book consists of 19 chapters, each dealing with a "controversial" subject. Some of the subjects are obviously controversial but a good many are not, at least not in the ordinary sense, since one can find hardly a subject in which there would not be a difference of opinion on one point or another. In the former category one can place "Prophylactic antiarrhythmic therapy in acute myocardial infarction," "Anticoagulant therapy for coronary heart disease" or "Indications for coronary artery surgery and patient selection." Examples of the latter category are "Serum digoxin level—Practical value," "Current concepts of hemiblocks" or "Echocardiography—Its practical value."

Seven of the 19 articles are written by the editor with the aid of his fellows and associates—acting as a jack of all trades. Most of the others are written by well-known authorities on the given subject. The problem here is that most of these authors have certain prejudices or commitments to a specific viewpoint—some even have vested interests in it—which makes it hardly possible to present a balanced view of the subject.

Disregarding the objectives of the book and reading some of the articles per se one can find excellent and informative summaries of less controversial subjects. However, in the light of the stated objectives of presenting the "pro and con" viewpoints in each chapter, the book is poorly conceived and badly executed. The editor's immodest postulate that "the book will be extremely valuable to all practicing physicians with various backgrounds" is not fulfilled and the book is not recommended.

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* * *

ENDOSCOPY—Edited by George Berci, MD, Director, Department of Endoscopy, Cedars-Sinai Medical Center, Los Angeles; Attending Surgeon, Wadsworth Veterans Administration Hospital, Los Angeles; Clinical Associate Professor, Department of Surgery, University of California, Los Angeles, School of Medicine; with 58 coauthors. Appleton-Century-Crofts, A Publishing Division of Prentice-Hall, Inc., 292 Madison Avenue, New York City (10017), 1976. 805 pages, $78.50.

This comprehensive and up-to-date reference work covers all aspects of endoscopy and should be of interest to persons in many different specialties. There are a few color plates that illustrate endoscopic findings, but certainly this book is not what one would consider a comprehensive atlas of endoscopic photographs. It is, rather, meant to be a thorough review of the technical aspects of endoscopy, and fills a definite need in this area.

The first part of the text relates to general principles of endoscopy. Such topics as optical principles; fiberoptic physics; light sources; various types of instruments, both rigid and fiberoptic; microbiology, and sterilization of endoscopes are included. In addition the technical aspects of ultrasound, laser beam surgical procedures and electrosurgery are covered in detail. Photography and television as they apply to endoscopy are also reviewed.

The second part of the book relates to clinical applications. The various types of gastrointestinal endoscopy are well covered, including newer procedures such as endoscopic polypectomy, choledochoscopy and retrograde cholangiopancreatography. Pediatric endoscopy as well as laparoscopy also are well covered. Sections on both gynecologic endoscopy and thoracic endoscopy are fairly extensive and procedures using both rigid and fiberoptic flexible instruments are discussed. Special topics including nephroscopy, arthroscopy, stereoencephaloscopy and retroperitoneoscopy are also covered. These subjects are discussed by specialists in their respective fields and there are 58 coauthors. It is a very readable book and should be an invaluable reference work.

JEAN K. HADDAD, MD, FACP
Associate Clinical Professor of Medicine
University of California Medical Center
San Francisco

* * *

THE MITRAL VALVE—A Pluridisciplinary Approach—Edited by Daniel Kalmanson, MD, Director of Clinical Teaching, Chief, Department of Cardiology, Cardiovascular Research Center ARNTIC, Foundation A. de Rothschild, Paris. Publishing Sciences Group Inc., 162 Great Rd., Acton, MA (01720), 1976. 576 pages, $25.00.

Daniel Kalmanson, MD, has collected in one book the major scientific papers presented at the International Symposium on the Mitral Valve held in Paris in May of 1975. His purpose is to present the latest information on the mitral heart valve acquired in many different disciplines and to integrate these data into one comprehensive work. The scientific papers which make up the 48 chapters of this book are divided into ten sections in a logical order of presentation. Each chapter is followed by a general discussion and a summary of important points.

Part one reviews the anatomy and physiology of the mitral valve apparatus and presents a new classification by Yacoula which permits accurate identification of individual chordae. The present trend toward a broader and more functional concept of the normal and the diseased mitral apparatus is presented. Part two discusses the pathology of natural and artificial mitral valves, including the prolapsing mitral valve leaflet syndrome. Parts three, four and five present pressure-flow relationships and motion of normal, diseased and artificial valves. The utilization of electromagnetic, ultrasonic and differential pressure transducer techniques for measuring blood velocity and blood flow across the mitral valve are discussed. The importance of a knowledge of instanteous mitral flow rate and velocity for understanding mitral valve physiology, pathophysiology and surgical correction is demonstrated. Emphasis is placed on new data obtained by electromagnetic, Doppler and ultrasonic investigations. Roelandt discusses pulsed, reflected ultrasound and Baker discusses the quantitation of mitral regurgitation using a gated Doppler technique.

The role of atrial and ventricular performances and particularly the time course and optimal timing for mitral valve operation is discussed in part 7. A major section of the work is devoted to artificial valves (Part 8), tissue valves (Part 9) and reconstructive surgical procedures on the natural heart valve (Part 10). The book concludes that the ideal prosthetic mitral valve remains to be developed and all of the types used at present are plagued by the risk of thromboembolic complications. Mitral valve replacement, therefore, should only be undertaken when all other possibilities are ruled out.

With tissue valves there is reported to be a lower risk of thromboembolism and anticoagulation is not required, but these valves do not possess the durability of prosthetic heart valves. Tissue valves are recommended for pulmonary and tricuspid valve replacement in all patients, for aortic and mitral valve replacement in women of child-bearing age, and for use in patients who may be difficult or dangerous to maintain on anticoagulation. Recognizing the inadequacy of both artificial and tissue valves, Drs. Carpentier (France), Dury and Angell (United States) maintain that as many as 40 percent of the mitral valve abnormalities need not be replaced but can in fact be repaired utilizing reconstructive surgical techniques. The technique of prosthetic ring annuloplasty described by Carpentier and co-workers represents a major accomplishment in mitral valve surgical operation. The procedure, however, may be technically more difficult to carry out correctly than valve replacement.

In spite of the wide range of the presentations and the complexity of the topics, the book provides an integrated approach to understanding the normal and abnormal mitral valvular apparatus. It is an important reference source for all those interested in the mitral valvular abnormalities.

ROBERT J. HENNING, MD
Assistant Professor of Medicine
University of Southern California
School of Medicine
Los Angeles

* * *

PERINATAL MEDICINE—4th European Congress of Perinatal Medicine—Edited by Z. K. Stembera, K. Polácek and V. Sabata; Co-editors: P. M. Dunn, H. F. R. Prechtl and E. Saling. Publishing Sciences Group Inc., 162 Great Rd., Acton, MA (01720), 1975. 556 pages, $25.00.

This book presents a series of abstracts from the biennial congress of the European Association of Perinatal Medicine held in 1974 in Prague, Czechoslovakia. The editors have chosen three of the major topics and included abstracts related to these topics along with the chairman's conclusions on each. The topics include (1) antenatal diagnosis of the "at risk" infant, (2) premature delivery and (3) preterm infant.

Czechoslovakia has a low perinatal mortality rate and so was an appropriate host country. Participation in this fourth congress showed the continued and significant growth of interests and organization of European perinatologists. The participants represented about every country in eastern and western Europe along with several American contributors.

Each major topic is given approximately equal length in this book. Considering the abstract format, the illustrations are very good; but as expected, the text, methods and references are limited. The abstracts on these topics represent a review of most of the techniques available in evaluating at-risk infants and touched on most of the current knowledge as of 1974. A series of papers evaluated at-risk infants at one, two, four and more years later. The concluding remarks appropriately noted many of the infants so identified turn out to be normal, so that further work is needed to better define those newborn infants with significant future risk factors.

The major problem with this type of publication is centered on its abstract form. This form, of necessity, is too brief to give anything but an overview of current work. The audience that would most benefit from this book would be perinatologists. I believe that in this book there is very little present dating from the 1974 congress that would be new to a perinatologist who keeps up with the literature.

DAVID H. DAIL, MD
Assistant Professor of Pathology
University of California, San Diego

REVIEW OF MEDICAL MICROBIOLOGY—Twelfth Edition—Ernest Jawetz, PhD, MD, Professor of Microbiology and Chairman, Department of Microbiology, Professor of Medicine, Lecturer in Pediatrics, University of California School of Medicine, San Francisco; Joseph L. Melnick, PhD, Distinguished Service Professor of Virology and Epidemiology, Baylor College of Medicine, Houston; Edward A. Adelberg, PhD, Professor of Human Genetics, Yale University School of Medicine, New Haven. Lange Medical Publications, Drawer L, Los Altos CA (94022), 1976. 542 pages, $10.00.

The new "Jawetz" maintains the familiar format of the previous issues. It commences with a useful and appropriate discussion of basic microbiology including the relationship of microorganisms to other groups of living organisms, structure and physiology, genetics, antimicrobial substances including disinfectants, germicides and antibiotics. A chapter on bacteriophage is also included in the first quarter of the book. Three concise, well-done chapters are devoted to immunology: host-parasite relationships, antigens and antibodies, and antibody- and cell-mediated immune reactions. These are followed by ten chapters specifically devoted to pathogenic bacteria, one on normal microbial flora of the body, one on pathogenic fungi (and actinomycetes), a chapter on diagnostic medical microbiology, 14 chapters on virology, and an appendix on medical parasitology.

In this 12th edition of the *Review of Medical Microbiology* is once again seen the fine updating characteristic of its predecessors. I have found this to be an extremely useful book but have some recurring concerns. In some parts, especially in the treatment of virology (202 pages), the term "review" in the title is somewhat of a misnomer. While Chapter 27 "General Properties of Viruses" is especially helpful, laying essential groundwork on classification, replication, pathogenesis and immunology, and the currentness of information is exemplary; for example, in the chapters on hepatitis and orthomyxo (influenza) virus, the depth of coverage in chapters 30 through 40 is excessive and out of keeping with the concept of a "review." A greater selectivity in dealing with the virology would be appropriate. Occasional other examples of this need can be cited; for example, there seems little justification for enumerating the alpha through delta hemolysins of Staphylococcus aureus.

The section on Pasteurellae (including Yersinia and Francisella) could be improved by dealing separately with each specific organism and corresponding disease. Also, it is time for the "Appendix: Medical Parasitology" to be accorded full status as a chapter. Reduction in the number or sizes, or both, of the illustrations of protozoa and helminths (they occupy 11 pages) so that diagrams of some life cycles could be included would improve this section.

Other minor suggested changes can be offered; for example, excision of the actinomycetes from the chapter on pathogenic fungi, inclusion of Bacteroides in Table 3-1 (principal groups of bacteria), placement of spectinomycin (an aminocyclitol) nearer the somewhat related other aminocyclitol (aminoglycoside) antibiotics; and the connection between metachromatic granules of corynebacteria (p. 192) and polyphosphate (volutin) (p. 9) should be made.

One concern expressed to me by medical students is that the *Review of Medical Microbiology* is difficult to read perhaps because of inclusion of so much information squeezed into a relatively small space and print. Careful editing with attachment of an appendix as a repository of the detail such as that cited above in connection with the virology section could enhance its usefulness and readability.

The foregoing criticisms are far outweighed by the benefits provided by the *Review of Medical Microbiology*. Drs. Jawetz, Melnick and Adelberg, and Lange Medical Publications have sustained the high quality work which continues to yield a fine, practical, up-to-date and reasonably priced textbook.

DEMOSTHENES PAPPAGIANIS, MD, PhD
Department of Medical Microbiology
University of California, Davis
School of Medicine

* * *

RECENT ADVANCES IN RHEUMATOLOGY—Part 1: Underlying Mechanisms of Disease—Part 2: Clinical Features and Treatment—Edited by W. Watson Buchanan, MD, FRCP, Professor of Medicine, Centre for Rheumatic Diseases and University Department of Medicine, Royal Infirmary, Glasgow; and W. Carson Dick, MD, MRCP, Honorary Clinical Lecturer, Department of Medicine, University of Glasgow, Consultant Physician, Centre for Rheumatic Diseases and University Department of Medicine, Royal Infirmary, Glasgow. Churchill Livingstone - Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. Part 1: 214 pages, $24.50; Part 2: 218 pages, $24.50.

In this attractive brace of volumes, the editors have conveniently divided recent basic developments in certain rheumatic diseases from clinical features and treatment. No attempt has been made to review the entire field of rheumatology, as has been done in Volume 19, No. 6, Supplemental, of *Arthritis and Rheumatism*. Rather, the focus has been directed at certain of the most significant advances. Utilizing the skills of a prestigious group of contributors, particularly from the United Kingdom and the United States, the editors have achieved an international flavor.

In part one, "Underlying Mechanisms of Disease," chapters are devoted to osteoarthrosis as a state of altered physiology (a departure from the hallowed "wear and tear" concept), amyloidosis, dermatomyositis and polymyositis, SLE in man and animals, experimental evaluation of immunosuppressive drugs in the context of connective tissue diseases, pathogenesis of autoimmune diseases, and the role of inflammatory mediators in joint inflammation.

Highlighting part two with an excellent selection of plates and figures, the authors and editors discuss the recent advances in the clinical features and treatment primarily of rheumatoid arthritis. Chapters are devoted to drug evaluation, including the latest nonsteroidal antiinflammatory agents as well as those of earlier vintage. Two chapters describe the various surgical procedures available for joints. Ocular hazards in connective tissue disease, including keratoconjunctivitis sicca, uveitis and scleritis, are discussed with clarity. Of particular importance is the final chapter, which concerns the relationship of the seronegative spondylarthritides to one of the most exciting developments in rheumatology—the histocompatibility antigen HLA-B27.

Both of these volumes are well organized and written. Although basic research scientists might find the discussions rather simplified, those engaged primarily in clinical rheumatology will welcome this approach. Part two should prove especially rewarding also to general physicians, orthopedic surgeons and students. Minor and unimportant negative criticisms would include the presence of fairly frequent typographical errors and the practice of some of the authors liberally to intersperse their sentences with the names of all cited references. In their zeal to give full credit, the contributors sometimes impair the free flow of syntax. In sum, however, these volumes are highly recommended.

RALPH W. SCHAFFARZICK, MD
Associate Clinical Professor of Medicine
Stanford University School of Medicine

in memoriam

Berry, Lorenzo Robert, Richmond. Died July 27, 1977 in Oakland of brain death-sepsis, aged 67. Graduate of Howard University College of Medicine, Washington, DC, 1935. Licensed in California in 1954. Dr. Berry was a member of the Alameda-Contra Costa Medical Association.

Boles, Albert, Oakland. Died August 20, 1977 in Oakland of complications of cerebrovascular accident, aged 85. Graduate of the University of Minnesota Medical School, Minneapolis, 1917. Licensed in California in 1922. Dr. Boles was a retired member of the Alameda-Contra Costa Medical Association.

Bulpitt, Helen Green, Santa Monica. Died July 13, 1977 in Santa Monica of cerebrovascular accident, aged 72. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1930. Licensed in California in 1930. Dr. Bulpitt was a member of the Los Angeles County Medical Association.

Bush, George. Los Angeles. Died June 27, 1977 in Santa Monica of leukemia, aged 63. Graduate of the University of Illinois College of Medicine, Chicago, 1937. Licensed in California in 1938. Dr. Bush was a member of the Los Angeles County Medical Association.

Chapman, Leland Stanford, Los Angeles. Died July 12, 1977 in Los Angeles of injuries received in traffic accident, aged 84. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1919, Licensed in California in 1966. Dr. Chapman was a member of the Los Angeles County Medical Association.

Cochems, Kenneth D., Los Angeles. Died April 8, 1977 in Van Nuys of heart disease, aged 78. Graduate of Rush Medical College, Chicago, 1923. Licensed in California in 1946. Dr. Cochems was a member of the Los Angeles County Medical Association.

Cole, Morton I., Los Angeles. Died June 10, 1977 in Los Angeles of heart disease, aged 70. Graduate of the University of Illinois College of Medicine, Chicago, 1935. Licensed in California in 1935. Dr. Cole was a member of the Los Angeles County Medical Association.

Collins, Marion C., Turlock. Died August 5, 1977 in Turlock, aged 70. Graduate of Northwestern University Medical School, Chicago, 1931. Licensed in California in 1931. Dr. Collins was a retired member of the Stanislaus Medical Society.

Collis, W. H. Langley, Stockton. Died March 27, 1977 of injuries received in an airplane crash, aged 73. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1932. Licensed in California in 1932. Dr. Collis was a member of the San Joaquin County Medical Society.

Fernandes, Carlos Freitas, Richmond. Died August 1, 1977 in Pope Valley, aged 83. Graduate of Faculdade de Medicina de la Universidade, de Lisboa, Lisbon, 1923. Licensed in California in 1927. Dr. Fernandes was a member of the Alameda-Contra Costa Medical Association.

Godman, Harold Everard, Santa Monica. Died March 23, 1977 in Anaheim, aged 56. Graduate of the University of Tennessee College of Medicine, Memphis, 1944. Licensed in California in 1949. Dr. Godman was a member of the Los Angeles County Medical Association.

Goldman, Theodore H., Beverly Hills. Died May 20, 1977 in Laguna Beach of cerebrovascular accident, aged 72. Graduate of Rush Medical College, Chicago, 1929. Licensed in California in 1929. Dr. Goldman was a retired member of the Los Angeles County Medical Association.

Gries, Louis, Long Beach. Died April 15, 1977 in Laguna Hills of heart disease, aged 86. Graduate of Loyola University School of Medicine, Chicago, 1922. Licensed in California in 1937. Dr. Gries was a retired member of the Los Angeles County Medical Association.

Haft, Albert J., Long Beach. Died August 1, 1977 in Long Beach of diabetes mellitus and uremia, aged 64. Graduate of Syracuse University College of Medicine, 1940. Licensed in California in 1951. Dr. Haft was a member of the Los Angeles County Medical Association.

Havard, Robert A., sr., Visalia. Died July 26, 1977 in Stanford University Hospital of leukemia, aged 53. Graduate of the University of Oregon Medical School, Portland, 1954. Licensed in California in 1955. Dr. Havard was a member of the Tulare County Medical Society.

Heissig, Ida, Los Angeles. Died July 11, 1977 in Tucson, aged 81. Graduate of the University of Illinois College of Medicine, Chicago, 1929. Dr. Heissig was a retired member of the Los Angeles County Medical Association.

Hsu, Hsia, Glendale. Died January 14, 1977 in Los Angeles, aged 50. Graduate of the National University of Taiwan College of Medicine, 1953. Licensed in California in 1970. Dr. Hsu was a member of the Los Angeles County Medical Association.

Jacobs, Melville L., Duarte. Died August 18, 1977 in Duarte, aged 72. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1931. Licensed in California in 1931. Dr. Jacobs was a member of the Los Angeles County Medical Association.

KALMAN, MANUEL, ROSS. Died July 28, 1977 in San Rafael, aged 74. Graduate of Boston University School of Medicine, 1926. Licensed in California in 1946. Dr. Kalman was an associate member of the Marin Medical Society.

KISTLER, CLARK C., Mountain View. Died August 7, 1977 in Los Altos of cancer, aged 55. Graduate of the Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, 1947. Licensed in California in 1967. Dr. Kistler was a member of the Santa Clara County Medical Society.

LOGAN, NOBLE HERALD, Lafayette. Died July 28, 1977 in Oakland of carcinoma of the pancreas, aged 77. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1927. Licensed in California in 1927. Dr. Logan was a retired member of the Alameda-Contra Costa Medical Association.

LUDINGTON, LOUIS GOODRICH, Los Angeles. Died December 15, 1976 of multiple myeloma, aged 56. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1949. Licensed in California in 1949. Dr. Ludington was a member of the Los Angeles County Medical Association.

LUNDEGAARD, EDWARD M., Oakland. Died August 22, 1977 in Oakland, aged 88. Graduate of Oakland College of Medicine and Surgery, 1912. Licensed in California in 1912. Dr. Lundegaard was a retired member of the Alameda-Contra Costa Medical Association.

MCPHERSON, WILLIAM HUMPHREY, Bakersfield. Died August 27, 1977 in Bakersfield of myocardial infarction. Graduate of the University of Alberta Faculty of Medicine, Edmonton, 1958. Licensed in California in 1959. Dr. McPherson was a member of the Kern County Medical Society.

MEADE, FRANK JOHN, Los Angeles. Died December 14, 1976 in Los Angeles, aged 83. Graduate of the College of Physicians and Surgeons, Medical Department, University of Southern California, Los Angeles, 1922. Licensed in California in 1922. Dr. Meade was a member of the Los Angeles County Medical Association.

MULLEN, RICHARD C., San Jose. Died August 9, 1977 in San Jose, aged 61. Graduate of the Creighton University School of Medicine, Omaha, 1944. Licensed in California in 1945. Dr. Mullen was a member of the Santa Clara County Medical Society.

ROYSTON, ERIC ATHERSTONE, Los Angeles. Died July 27, 1977 in Los Angeles of cancer, aged 84. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1925. Licensed in California in 1925. Dr. Royston was a retired member of the Los Angeles County Medical Association.

SHOEMAKER, ROSEMARY (ROSEMARY SHOEMAKER KAHLER), Los Angeles. Died May 12, 1977 of uremia following treatment of ruptured appendix, aged 67. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1933. Licensed in California in 1933. Dr. Shoemaker was a retired member of the Los Angeles County Medical Association.

SINK, FENTON HOMER, JR., Lancaster. Died January 1, 1977 in Lancaster, aged 56. Graduate of the University of Southern California School of Medicine, Los Angeles, 1951. Licensed in California in 1951. Dr. Sink was a member of the Los Angeles County Medical Association.

SMITH, LEMON, Fontana. Died August 8, 1977 in Elsinore of ruptured acute myocardial infarction, aged 50. Graduate of Meharry Medical College, Nashville, 1952. Licensed in California in 1960. Dr. Smith was a member of the San Bernardino County Medical Society.

TINETTI, ERNEST FRANK, Van Nuys. Died July 6, 1977 in Encino of acute myocardial infarction, aged 69. Graduate of the University of Nebraska College of Medicine, Omaha, 1936. Licensed in California in 1947. Dr. Tinetti was a member of the Los Angeles County Medical Association.

VAN MAREN, HAROLD B., Oakland. Died June 19, 1977 in Oakland, aged 46. Graduate of the College of Osteopathic Medicine and Surgery, Des Moines, 1959. Licensed in California in 1960. MD degree from California College of Medicine, 1962. Dr. Van Maren was a member of the Alameda-Contra Costa Medical Association.

WARREN, JAMES PAUL, San Francisco. Died August 5, 1977 in Daly City, aged 81. Graduate of the University of California Medical School, Berkeley-San Francisco, 1925. Licensed in California in 1925. Dr. Warren was a retired member of the San Francisco Medical Society.

ZWENG, HAROLD CHRISTIAN, Palo Alto. Died August 26, 1977 in Stanford Hospital of cerebrovascular accident, aged 54. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1949. Licensed in California in 1954. Dr. Zweng was a member of the Santa Clara County Medical Society.

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(Continued on Page 24)

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(Continued from Page 22)

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(Continued from Page 19)

INFERTILITY—A Guide for the Childless Couple—Barbara Eck Menning. Prentice-Hall, Inc., Englewood Cliffs, NJ (07632), 1977. 178 pages, no price given.

INFORMED CONSENT TO HUMAN EXPERIMENTATION: The Subject's Dilemma—George J. Annas, JD, MPH, Director, Boston University Center for Law and Health Sciences; Assistant Professor, Boston University School of Medicine; Leonard H. Glantz, JD, Staff Attorney, Center for Law and Health Sciences, Boston University School of Law; Assistant Professor, Department of Socio-Medical Sciences, Boston University School of Medicine; and Barbara F. Katz, JD, Instructor, Boston University School of Law. Ballinger Publishing Company, 17 Dunster St., Cambridge, MA (02138), 1977. 334 pages, $17.50.

LUPUS ERYTHEMATOSUS—Second Edition, Revised—Edited by Edmund L. Dubois, MD, Clinical Professor of Medicine, Clinical Immunology and Rheumatic Disease Section, Department of Medicine, University of Southern California School of Medicine; Director of the "Collagen Disease" Clinic, Los Angeles County/University of Southern California Medical Center, Los Angeles,. University of Southern California Press, Los Angeles, CA (90007), 1976. 798 pages, $39.50. (Address all inquiries to: Edmund L. Dubois, MD, Editor, USC School of Medicine, 2025 Zonal Ave., Los Angeles, CA 90033.)

THE MAKING OF A MEDICARE DOCTOR—John M. Larham, MD. Vantage Press, Inc., 516 West 34 Street, New York, NY (10001), 1977. 88 pages, $5.95.

THE MENACE OF MADNESS IN HIGH PLACES—Russel V. Lee, MD, Founder of Palo Alto Medical Clinic. Omega Books, 428 Tamal Plaza, Corte Madera, CA (94925), 1977. 204 pages, $6.50.

MICROVASCULAR RECONSTRUCTIVE SURGERY—Bernard McC. O'Brien, BSc, MS(Melb), FRCS(Eng), FRACS, FACS, Director, Microsurgery Research Unit, and Assistant Plastic Surgeon, St. Vincent's Hospital, Melbourne; Hunterian Professor, Royal College of Surgeons of England; Kazanjian Professor, New York University Medical Center; Consultant Plastic Surgeon to Royal Australian Air Force and to Mercy Maternity Hospital, Melbourne; Senior Research Fellow, Department of Ophthalmology, University of Melbourne. Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th Street, New York City (10036), 1977. 360 pages, $38.00.

THE NERVOUS SYSTEM—William F. Ganong, MD, Professor and Chairman, Department of Physiology, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1977. 226 pages, $8.00.

NO GRAVY ON THE VEST—The Art of Growing Old in Style—Russel V. Lee, MD, Founder of Palo Alto Medical Clinic. Omega Books, 428 Tamal Plaza, Corte Madera, CA (94925), 1976. 113 pages, $4.00 (paperback).

PAEDIATRIC HAEMATOLOGY—Michael L. N. Willoughby MA, MD, MRC Path, Consultant Haematologist to the Royal Hospital for Sick Children and Queen Mother's Hospital, Glasgow, Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th Street, New York City (10036), 1977. 434 pages, $39.50.

PLEASE REMEMBER ME—Mari Brady. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1977. 104 pages, $5.95.

PSYCHOSOMATIC MEDICINE—Its Clinical Applications—Edited by Eric D. Wittkower, MD, LRCP, LRCS, LRFPS, FRCPS, FRCP(C), Professor Emeritus, Department of Psychiatry, McGill University; Consulting Psychiatrist, Royal Victoria Hospital, Montreal General Hospital and Queen Elizabeth Hospital, Montreal; and Hector Warnes, BSc, MD, FRCP(C), FAPA, Professor and Chairman, Department of Psychiatry, University of Dublin, Trinity College; Clinical Director, Department of Psychiatry, St. James's Hospital; Consultant Psychiatrist, St. Patrick's Hospital and Sir Patric Dun's Hospital, Dublin. Harper & Row, Publishers, Inc., Medical Department, 2350 Virginia Avenue, Hagerstown, MD (21740), 1977. 356 pages, $19.95.

QUESTIONS AND ANSWERS ABOUT ACNE—John R. T. Reeves, MD, Assistant Clinical Professor of Dermatology, University of California, San Francisco; Assistant Chief of Dermatology, San Francisco General Hospital. Prentice-Hall, Inc., Englewood Cliffs, NJ (07632), 1977. 111 pages, $5.95.

RECENT ADVANCES IN CLINICAL VIROLOGY—Number 1—Edited by A. P. Waterson, MD(Cantab), FRCP(Lond), FRCPath, Professor of Virology, Royal Postgraduate Medical School, University of London, Consultant Virologist, Hammersmith Hospital. Longman Inc., 19 West 44th St., New York City (10036), 1977. 200 pages, $22.00.

RECENT ADVANCES IN BLOOD COAGULATION—Number Two—Edited by L. Poller, Consultant Haematologist, Withington Hospital, University Hospital of South Manchester, and Director, National Reference Laboratory for Anticoagulant Control Reagents (World Health Organization Collaborating Center), Manchester. Churchill Livingston—Medical Division, Longman Inc., 19 West 44th St., New York City (10036), 1977. 388 pages, $35.00.

RECENT ADVANCES IN DERMATOLOGY—Number Four—Edited by Arthur Rook, MD, FRCP, Consultant Dermatologist, Addenbrooke's Hospital, Cambridge; Civil Consultant in Dermatology to the Royal Air Force. Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th Street, New York City (10036), 1977. 395 pages, $27.50.

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CANCER

November 18-19—**Endocrine Aspects of Cancer: New Perspectives.** Mt. Zion Hospital and Medical Center, San Francisco. Friday-Saturday. Contact: Ann Raisbeck, Dept. of Med. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2401.

December 3—**Physicians' Symposium on the Psychosocial Care of the Cancer Patient.** American Cancer Society, Alameda County Unit, at Claremont Hotel, Berkeley. Saturday. Contact: Robert Wooster, Ed. Dir., ACS, 1212 Broadway, Suite 612, Oakland 94602. (415) 832-7012.

January 27-28—**Cancer.** Peralta Hospital at Kaiser Center, Oakland. Friday-Saturday. Contact: Tish Hammerlee, Peralta Hosp., 450 30th St., Oakland 94609. (415) 451-4900, ext. 264.

January 30-31—**Cancer.** USC. Monday-Tuesday.

March 9-12—**Modern Concepts in Oncology.** UCLA at Canyon Hotel, Palm Springs. Thursday-Sunday.

March 10-12—**Cancer Endodurietherapy.** USC at Hotel Bonaventure, Los Angeles. Friday-Sunday. 22 hrs.

March 27-31—**Cancer.** STAN. Monday-Friday. 27 hrs. $265.

EMERGENCY MEDICINE

October 24-28—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday.

November 8-10—**American College of Emergency Physicians—5th Annual Scientific Assembly.** Hilton Hotel, San Francisco. Tuesday-Thursday. 23 hrs. Contact: Meeting Registrar, ACEP, 3900 Capital City Blvd., Lansing, MI 48906. (517) 321-7911.

December 8-9—**Advances in Emergency Medicine—Metabolic Emergencies.** UCSF. Thursday-Friday.

December 12-16—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Islandia Hotel, San Diego. Monday-Friday.

January 23-27—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Town and Country Convention Center, San Diego. Monday-Friday. 40 hrs. $325.

January 23-27—**Topics in Emergency Medicine.** UCSF at Ralph K. Davies Medical Center, San Francisco. Monday-Friday.

March 20-24—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday. 40 hrs. $325.

MEDICINE

October 18—**Metabolic Diseases.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Chr., Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

October 21-22—**Internal Medicine Symposium—22nd Annual.** Southern Calif. Permanente Medical Group at Hilton Hotel, Pasadena. Friday-Saturday. Contact: Shirley Gach, So. Calif. Permanente Med. Grp., 4900 Sunset Blvd., Rm. 6014, Los Angeles 90027. (213) 667-4241.

October 21-23—**Practical Cardiology—1977.** American College of Cardiology at Del Monte Hyatt Hotel, Monterey. Friday-Sunday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Division of Continuing Education, ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

October 25-27—**Workshop on Methods of Quantitative Immunoelectrophoresis.** UCSD at La Jolla Village Inn and VA Hospital, San Diego. Tuesday-Thursday. 20 hrs.

October 26—**Consultations in Hypertensions.** UCSD at Vacation Village, San Diego. Wednesday.

October 28-29—**Diabetes.** Palo Alto Medical Clinic, STAN and Santa Clara County Diabetes Society at Palo Alto Medical Clinic. Friday-Saturday. 9 hrs. $50. Contact: William McKee, MD, Palo Alto Medical Clinic, 300 Homer Ave., Palo Alto 94301. (415) 321-4121.

October 30-November 3—**American College of Chest Physicians—43rd Annual Scientific Assembly.** MGM Grand Hotel, Las Vegas. Sunday-Thursday. Contact: Dale E. Braddy, MS, Dir. of Education, ACCP, 911 Busse Highway, Park Ridge, IL 60068.

(Continued on Page 31)

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

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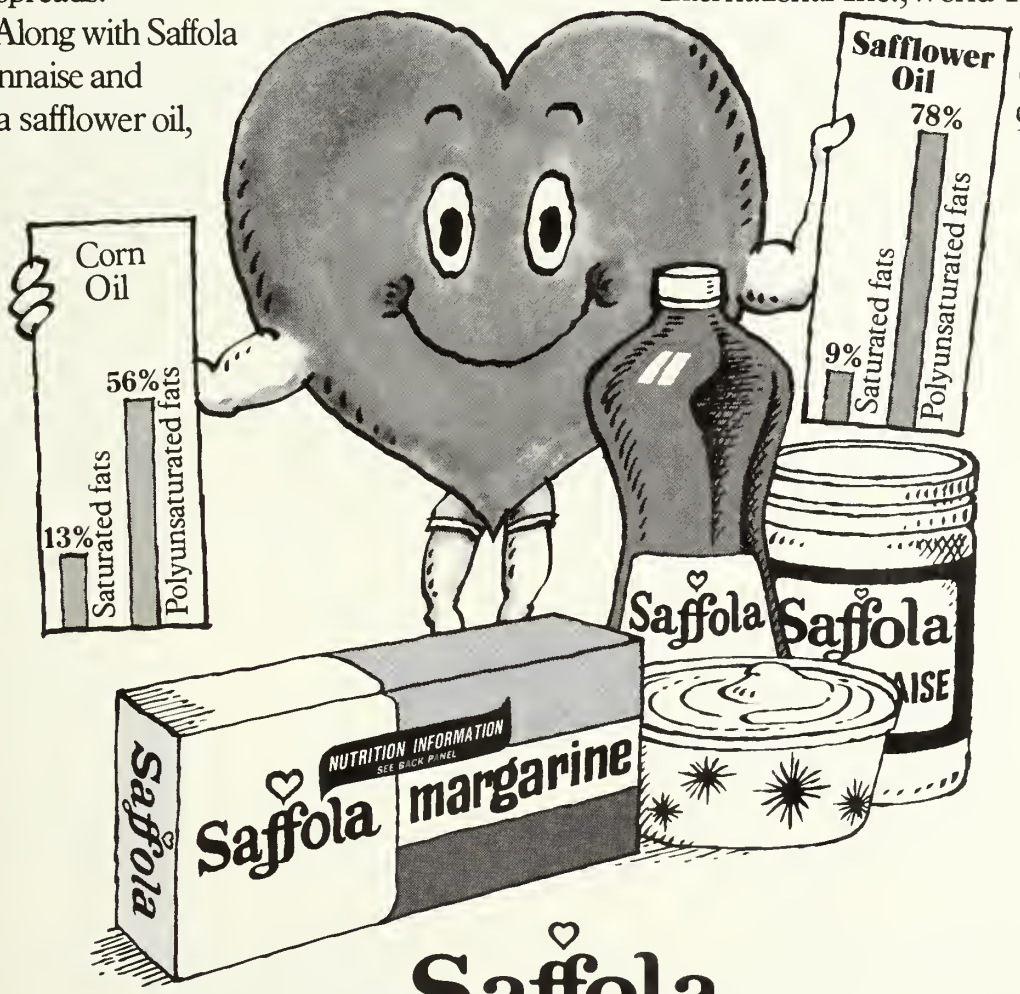

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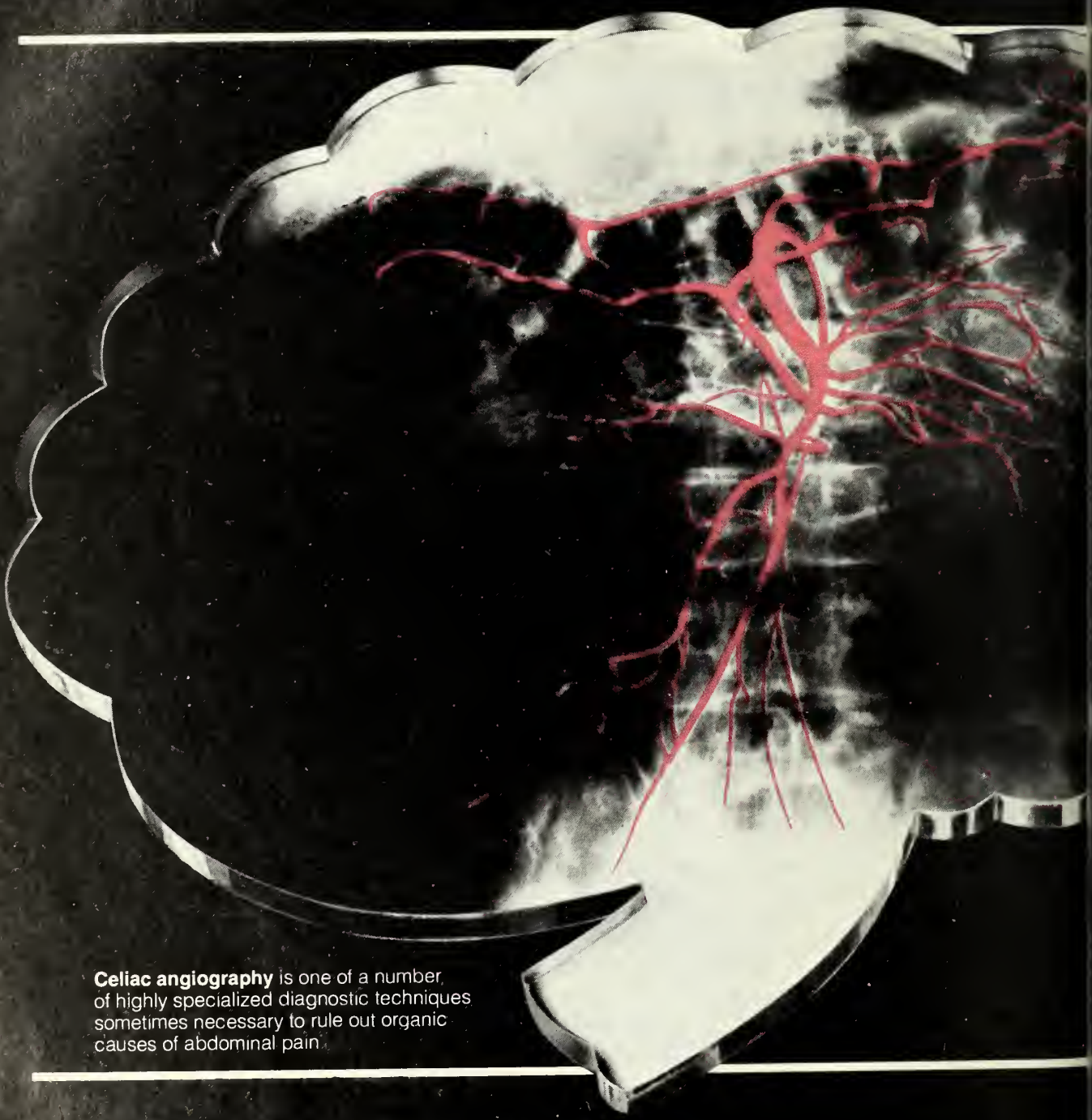

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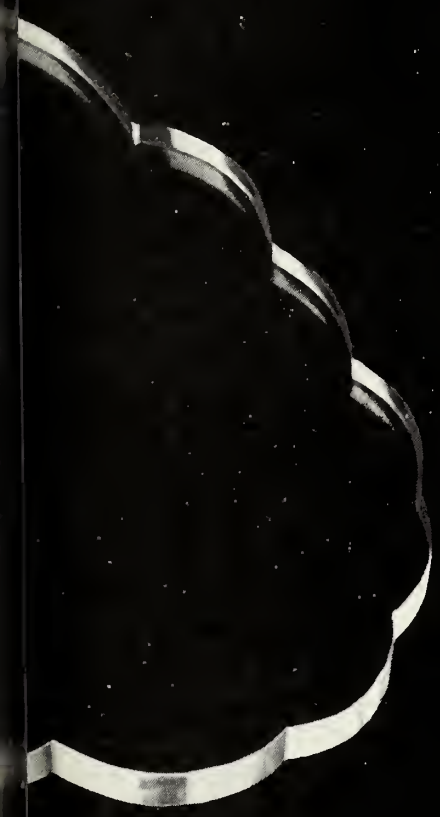

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Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergic drugs, an inhibiting effect on lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude development of ataxia, oversedation or confusion (not more than two capsules per day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacologic effects of agents, particularly potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: No side effects or manifestations not seen with either compound alone have been reported with Librax. When chlordiazepoxide hydrochloride is used alone, drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are avoidable in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally with chlordiazepoxide hydrochloride, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax are typical of anticholinergic agents, *i.e.*, dryness of the mouth, blurring of vision, urinary hesitancy and constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

Dosage: Individualize for maximum beneficial effects. Usual maintenance dose is 1 or 2 capsules, 3 or 4 times a day, before meals and at bedtime. Geriatric patients—see Precautions.

How Supplied: Librax is available in green capsules, each containing 5 mg chlordiazepoxide hydrochloride (Librium®) and 2.5 mg clidinium bromide (Quarzan®)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50, available singly and in trays of 10.

ROCHE

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(Continued from Page 26)

November 3-6—**California Society of Internal Medicine—Annual Meeting.** Canyon Hotel, Palm Springs. Thursday-Sunday. Contact: CSIM, 703 Market St., Suite 1412, San Francisco 94103. (415) 362-1548.

November 4-5—**Mechanisms of Hemostasis and Thrombosis: Experimental and Clinical Perspectives.** PMC at Fairmont Hotel, San Francisco. Friday-Saturday.

November 7-11—**Pediatric Allergy and Clinical Immunology.** UCSF. Monday-Friday.

November 7-16—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. 10 days. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Division of Continuing Education, ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

November 9—**Endocrinology Seminar.** LLU. Wednesday. 4 hrs. $25.

November 10-12—**Diagnosis and Management of Diseases of Peripheral Nerves and Muscle.** UCSD at Hilton Hotel, San Diego. Thursday-Saturday. 14 hrs. $125.

November 17-19—**Unusual Problems in Pulmonary Disease.** USC at Erawan Gardens, Palm Springs. Thursday-Saturday.

November 26-December 3—**Lymphoproliferative Disorders.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

December 2-3—**Current Concepts in Renal Disease—7th Annual Medical Staff Symposium.** Daniel Freeman Hospital at Hyatt House Hotel, Los Angeles. Friday-Saturday. 9 hrs. $80. Contact: Donald Dennis, PhD, Dir. of Med. Ed., Daniel Freeman Hosp., 333 N. Prairie, Inglewood 90301. (213) 674-7050, ext. 127.

December 2-4—**Advances in Heart Disease—1978.** American College of Cardiology at Fairmont Hotel, San Francisco. Friday-Sunday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Division of Continuing Education, ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

December 5-9—**Advances in Diagnosis and Treatment in Clinical Medicine.** American College of Physicians, Harbor General Hospital and St. Mary's Medical Center at Hyatt House Hotel, Los Angeles. Monday-Friday. Contact: Registrar, ACP, 4200 Pine St., Philadelphia, PA 19104.

December 7—**Current Data on the Epidemiology and Clinical Management of Essential Hypertension—Dinner Meeting/Scientific Program.** L. A. Soc. of Internal Medicine at L. A. County Medical Assn., Los Angeles. Wed. 1½ hrs. $7.50. Contact: Thomas T. Yoshikawa, MD, Prog. Chr., LASIM, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

December 10—**Pulmonary Artery Catheters and Ventilators.** PMC. Saturday. 6 hrs. $300.

December 12—**Current Concepts in Ileitis and Colitis.** UCD at Red Lion Motor Inn, Sacramento. Monday.

December 14—**Degenerative Diseases of the Aorta—3rd Annual Lyman A. Brewer III Cardiothoracic Symposium.** White Memorial Medical Center at Century Plaza Hotel, Century City. Wednesday. 8 hrs. $50. Contact: Howard Whigman, PhD, Coor., Cont. Med. Ed., White Memorial Med. Ctr., 1720 Brooklyn Ave., Los Angeles 90033.

January 4-March 15—**Nights at UCLA: Infectious Diseases for the Practicing Internist.** Wednesdays; 7:30-9:30 p.m. 22 hrs. $200.

January 11—**Management of Arrhythmias.** LLU. Wednesday. 4 hrs. $25.

January 20-21—**Stress Testing: A New Look Forward to New Developments—Backward to Old Concepts.** American College of Cardiology at Memorial Hospital Medical Center, Long Beach. Friday-Saturday. Contact: Miss Mary Ann McInerny, Dir., Extramural Programs Dept., Div. of Cont. Ed., ACC, 911 Old Georgetown Rd., Bethesda, MD 20014.

January 21—**Systemic Disease/Eye, Mouth, Skin Manifestations.** See Of Interest to All, January 21.

January 24-27—**Present Concepts in Internal Medicine.** American College of Physicians at Letterman Army Medical Center, San Francisco. Tuesday-Friday. Contact: Registrar, ACP, 4200 Pine St., Philadelphia, PA 19104.

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Space is limited, so register early.

January 25-27—**Advances in Neurology.** UCSF at Hyatt on Union Square, San Francisco. Wednesday-Friday.

January 27-29—**New Frontiers on the Relationships of Lipids, Lipoproteins and the Arterial Wall in Cardiovascular Disease.** UC Extension, Berkeley, and UCSF at Hyatt on Union Square, San Francisco. Friday-Sunday. 12 hrs. $150. Contact: Medical Symposia, Div. of Letters and Sciences, UC Extension, Berkeley 94720. (415) 642-1061.

January 28—**Management of Fluid, Electrolyte and Acid-Base Disorders.** STAN. Saturday. 7 hrs.

February 7-10—**Your Consultant Speaks—A Multidisciplinary Course for Dermatologists.** STAN at Lake Tahoe. Tuesday-Friday. 12 hrs. $225; $100 for residents and those in training.

February 15-17—**Recent Advances in Gastroenterology.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday.

February 23-25—**Advances in the Diagnosis and Therapy of Cardiovascular Disease—1978.** American College of Cardiology at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed. ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 6-9—**American College of Cardiology—27th Annual Scientific Session.** Disneyland Hotel, Anaheim. Monday-Thursday. Contact: Patrick Ziarnik, Dir., Annual Sci. Session Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 10-11—**Clinical Cardiology.** American College of Cardiology at Kauai Surf Hotel, Kauai, Hawaii. Friday-Saturday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 16-19—**Viral Hepatitis.** UCSF at Hilton Hotel, San Francisco. Thursday-Sunday. 26 hrs. $145.

March 23-25—**Immunology and Allergy Conference—2nd Annual.** UCSD at Hilton Hotel, San Diego. Thursday-Saturday.

March 28-31—**Consultant's Course in Dermatology—6th Annual.** UCSF. Tuesday-Friday.

March 31-April 1—**Seminar on Thrombosis.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday.

OBSTETRICS AND GYNECOLOGY

October 17-21—**Obstetrics/Gynecology Review.** USC at Beverly Hilton Hotel, Beverly Hills. Monday-Friday.

October 28—**Advances in Obstetrics and Gynecology—11th Annual Meeting.** Northern Calif. Obstetrical and Gynecological Society at Red Lion Motor Inn, Sacramento. Friday. 7 hrs. Contact: Benjamin J. Berry, MD, Prog. Chr., NCOGS, 3720 Mission Ave., Carmichael 95608. (916) 481-5401.

November 10-12—**Menopause, Fetal Monitoring, and Genetics.** UCSF at Mark Hopkins Hotel, San Francisco. Thursday-Saturday.

November 12-14—**Comprehensive Laparoscopy: Current Principles and Practice.** UCSD at Kona Kai Club, Kona, Hawaii. Saturday-Monday.

November 12-19—**Endocrinology—Infertility.** UCSF at Kaui Surf, Kaui, Hawaii. One week.

December 1-3—**High-Risk Pregnancy—2nd Annual Postgraduate Course.** Memorial Hospital Medical Center of Long Beach at Canyon Hotel, Palm Springs. Tuesday-Saturday. 14½ hrs. $200. Contact: Exec. Sec., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 14-21—**Perinatal Medicine.** USC at Royal Lahaina, Maui, Hawaii. One week.

January 28-30—**Comprehensive Laparoscopy.** UCSD at Kona Kai Club, San Diego. Saturday-Monday. 16 hrs. $375.

February 11-12—**Obstetrical and Gynecological Forum.** L. A. Obstetrical and Gynecological Society at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. Contact: Ms. Dee Davis, Exec. Sec., L. A. Obstetrical and Gynecological Society, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

PEDIATRICS

October 15-22—**Pediatrics for the Practitioner.** Children's Hospital of Long Beach and American Academy of Pediatrics, Chapter 2, at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. Contact: Margaret Frederick, Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 21-22—**Adolescence Sexuality and Related Problems.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday.

November 4-5—**Children's Experiences of Health and Illness.** UCD at Claremont Hotel, Berkeley. Friday-Saturday.

November 7-11—**Pediatric Allergy and Clinical Immunology.** See Medicine, November 7-11.

November 15—**Pediatrics—Common Office Problems and Treatment.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Chr., Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

December 3—**Practical Aspects of Sports Medicine for Pediatricians.** American Academy of Pediatrics, Calif. Chapter I, Dist. IX, at Union Square Holiday Inn, San Francisco. Saturday. Contact: Martin Gershman, MD, 595 Buckingham Way, San Francisco 94132.

January 12-14—**General Pediatrics.** American Academy of Pediatrics at Kona Surf Hotel, Kailua-Kona, Hawaii. Thursday-Saturday. Contact: L. J. Nagel, Dept. of Cont. Ed., AAP, P.O. Box 1034, Evanston, IL 60204. (312) 869-4255.

January 26-28—**Troubled Youth.** See Psychiatry, January 26-28.

January 27-29—**Pediatric Anesthesiology.** See Surgery and Anesthesiology, January 27-29.

January 28-29—**Pediatrics for the Primary Physician: A Practical Update.** See Of Interest To All, January 28-29.

February 10—**Pediatric Otolaryngology.** See Surgery and Anesthesiology, February 10.

PSYCHIATRY

October 25, November 1, 8, 15, 22—**Psychoanalytic Approach to Problem Patients.** So. Calif. Psychoanalytic Institute at Pasadena. 5 Tuesday evenings; 10 hrs. $50. Contact: Mrs. Alva Lane, Extension Div., So. Calif. Psychoanalytic Institute, 9024 Olympic Blvd., Beverly Hills 90211. (213) 276-2455.

November 4-5—**Update on the Major Handicaps: Clinical and Psychosocial Aspects.** See Of Interest To All, November 4-5.

November 13-16—**Academy of Psychosomatic Medicine.** South Coast Plaza Hotel, Costa Mesa. Sunday-Wednesday. 22 hrs. Contact: Mark C. Lukas, APM, 4902 Tollview Dr., Rolling Meadows, IL 60008. (312) 398-3140.

November 14-18—**Group Therapy Seminars.** UCSF at Merritt Hotel, Oakland. Monday-Friday.

January 10-March 21—**Intensive Review of Psychiatry.** USC. Tuesday evenings.

January 20-22—**Psychoanalytically Oriented Psychotherapy: A Retrospective.** UCSF. Friday-Sunday.

January 26-28—**Troubled Youth.** USC at Vacation Village, San Diego. Thursday-Saturday.

January 29-February 3—**Midwinter Program in Continuing Education for Psychiatrists.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday.

February 8—**Psychiatry Seminar.** LLU. Wednesday. 4 hrs. $25.

RADIOLOGY AND PATHOLOGY

October 21-23—**Society of Nuclear Medicine—2nd Annual Western Regional Meeting.** Aladdin Hotel, Las Vegas. Friday-Sunday. Contact: Justine J. Lynch, P.O. Box 40279, San Francisco 94140. (415) 647-0722 or (415) 647-5909.

November 2-4—**Gram Negative Organisms: An Approach to Identification.** Memorial Hospital Medical Center, Long Beach. Wednesday-Friday. 16 hrs. $100. Contact: Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

December 20—**Diagnostic X-Ray Including Cat Scans.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Chr., Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

January 16-20—**Computed Tomography.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. $295.

January 17—**Updating Radiation Therapy.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Chr., Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

January 27-29—**Los Angeles Radiological Society—13th Annual Mid-Winter Meeting.** Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Nathan Green, MD, 15107 Varnowen St., Van Nuys 91405.

January 27-29—**New Frontiers on the Relationships of Lipids, Lipoproteins and the Arterial Wall in Cardiovascular Disease.** See Medicine, January 27-29.

February 19-24—**Interpretative Enzymology.** UCSD at Sheraton Inn-Airport, San Diego. Sunday-Friday. 25 hrs.

February 21—**Clinical Laboratory Tests: Results, Clinical Application and New Laboratory Tests.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Chr., Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

March 4-5—**Diagnostic Nuclear Imaging.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

March 6-10—**Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. $275.

March 11-12—**A Practical Course in B-Scan Ultrasound.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

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SURGERY AND ANESTHESIOLOGY

October 21-22—**Trauma: Immediate Care.** UCSF. Friday-Saturday.

October 23-November 4—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200 for otolaryngologists; $900, residents. Contact: Malcolm D. Graham, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

October 28-29—**The Macula.** Retina Research Fund of St. Mary's Hospital and Medical Center at Hyatt on Union Square, San Francisco. Friday-Saturday. Contact: Claire Ohiyon, c/o Howard Schatz, MD, 3637 Sacramento St., San Francisco 94118. (415) 921-4860.

October 30-November 4—**American Society of Plastic and Reconstructive Surgeons—Annual Convention.** Hilton Hotel, San Francisco. Sunday-Friday. 33 hrs. Contact: Linda Campbell, ASPRS, 29 E. Madison St., Chicago 60602. (312) 641-0593.

November 3-5—**Nerve Repair: Clinical and Experimental Basis.** UCSF. Thursday-Saturday.

November 5—**Review of Retinal Disease and Surgery.** The Retina Research Fund of St. Mary's Hospital at Hyatt on Union Square, San Francisco. Saturday. 7 hrs. Contact: Howard Schatz, MD, 3637 Sacramento St., San Francisco 94118.

November 12—**Current Concepts in Ophthalmic Plastic Surgery.** Jules Stein Eye Institute, Los Angeles. Saturday. Contact: Shelley E. Reid, Jules Stein Eye Institute, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

November 17-18—**Legg-Calve-Perthes Symposium.** Orthopaedic Hospital, Los Angeles, at Airport Park Hotel, Inglewood. Thursday-Friday. $200. Contact: Med. Ed. Dept., Orthopaedic Hospital, 2400 S. Flower St., Los Angeles 90007.

November 18-19—**Strabismus.** PMC. Friday-Saturday. 16 hrs.

November 19-20—**American Society of Anesthesiologists—Regional Refresher Course.** Sahara Hotel, Lake Tahoe. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

November 30-December 2—**Annual Ophthalmology Program.** UCSF. Wednesday-Friday.

November 30-December 2—**Applied Biomechanics for Orthopedic Surgeons.** UCLA. Wednesday-Friday. 23 hrs. $200.

December 2-4—**ENG Workshop.** PMC at Ilikai Hotel, Honolulu. Friday-Saturday. 24 hrs. $395.

December 3—**Emergency Anesthesia.** Sacramento Valley Anesthesia Society; UCD; Calif. Society of Anesthesiologists at Red Lion Motor Inn, Sacramento. Saturday. $50. Contact: John H. Eisele, MD, Dept. of Anesthesiology. UCD Sch. of Med., Davis 95616. (916) 752-2703.

December 14—**Treatment of Parkinsonism and Modern Concepts.** LLU. Wednesday. 4 hrs. $25.

January 5-7—**Anesthesia Update '78.** UCSD at Hotel Del Coronado, Coronado. Thursday-Saturday. 15 hrs. $150.

January 16-20—**Otologic Surgery—13th Annual Course.** Ear Research Institute, Los Angeles. Monday-Friday. 45 hrs. $500. Contact: F. H. Linthicum, Jr., MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

January 22-26—**Ophthalmology and Otolaryngology—47th Annual Mid-Winter Clinical Convention.** The Research Study Club of Los Angeles, Inc., at Hilton Hotel, Los Angeles. Sunday-Thursday. 28 hrs. $175. Contact: Mr. Richard Pruter, Exec. Sec., P. O. Box 49412, Los Angeles 90049. (213) 879-0143.

January 27-29—**Pediatric Anesthesiology—16th Clinical Conference.** Children's Hospital of Los Angeles at Hilton Hotel, Los Angeles. Friday-Sunday. 15 hrs. $135. Contact: Wayne Herbert, MD, Children's Hosp., 4650 Sunset Blvd., Los Angeles 90027. (213) 660-2450, ext. 2262.

February 5-8—**Surgical Anatomy—19th Annual Theodor Billroth Course.** LLU. Sunday-Wednesday. 32 hrs. $200.

February 10—**Pediatric Otolaryngology.** USC. Friday.

February 28-March 3—**Diagnosis and Management of Acoustic Neuromas and Skull Base Tumors.** Ear Research Institute, Los Angeles. Tuesday-Friday. 32 hrs. $400. Contact: William F. House, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

March 2-3—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs.

March 8—**General Surgery Seminar.** LLU. Wednesday. 4 hrs. $25.

March 9-10—**The Orbit: Diagnostic Approaches and Management Decisions.** PMC at Stanford Court Hotel, San Francisco. Thursday-Friday. $225.

March 12-17—**Anesthesiology 1978—4th Annual Winter Meeting.** Anesthesiology Educational Foundation and Calif. Society of Anesthesiologists at Mammoth Lakes. Sunday-Friday. 20 hrs. Contact: Ronald L. Katz, MD, Dept. of Anesthesiology, UCLA School of Medicine, Los Angeles 90024.

March 19-23—**International Anesthesia Research Society—52nd Congress.** Hilton Hotel, San Francisco. Sunday-Thursday. Contact: B. B. Sankey, MD, Exec. Sec., IARS, 3645 Warrensville Center Rd., Cleveland, OH 44122. (216) 295-1124.

March 21—**Urology—Common Office Problems and Treatment.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Chr., Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

March 29-April 2—**Controversial Areas in Surgery—15th Annual Seminar.** UCLA at Canyon Hotel, Palm Springs. Wednesday-Sunday. 13 hrs. $195.

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OF INTEREST TO ALL PHYSICIANS

October 15, 19, 26, November 2, 9—**Caring for the Patient as a Human Being.** UC Extension, Berkeley, and Institute for the Study of Humanistic Medicine at UC Extension Center, San Francisco. Saturday and four Wednesday afternoons. Contact: Letters and Sciences, UC Extension, 2223 Fulton St., Berkeley 94720. (415) 642-1061.

October 17-21—**Family Practice Review—2nd Annual.** LLU. Monday-Friday. 30 hrs. $150.

October 19-22—**American Society of Human Genetics—28th Annual Meeting.** ASHG and UCSD at Vacation Village, San Diego. Wednesday-Saturday. Contact: UCSD

October 22—**Selected Topics on Infectious Disease.** PMC. Saturday. 6 hrs. $80.

October 27-28—**Living with Chronic and Terminal Illness.** PMC. Thursday-Friday. 6 hrs. $60.

October 29—**Audiology Update for Primary Care Physicians.** PMC. Saturday. 6 hrs. $80.

October 29—**Hormones and Sexuality, Part II.** UCLA. Saturday. $65 for both parts; $35, one part.

October 30-November 3—**American Medical Association—Regional Meeting.** Sheraton Waikiki, Honolulu, Hawaii. Sunday-Thursday. Contact: AMA, 535 N. Dearborn, Chicago 60610.

October 31-November 4—**Intensive Care.** STAN. Monday-Friday.

November 4-5—**Update on the Major Handicaps: Clinical and Psychosocial Aspects.** UCSF. Friday-Saturday. 12 hrs.

November 5—**Current Concepts of Gonococcal Disease—Dinner Meeting/Scientific Program.** L. A. Society of Internal Medicine at L. A. County Med. Assn., Los Angeles. Saturday. 1½ hrs. $7.50. Contact: Thomas T. Yoshikawa, MD, LASIM, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

November 5-6—**Practical Rheumatology for the Primary Care Physician.** UCLA and Arthritis Foundation, Southern California Chapter, at UCLA. Saturday-Sunday. 12 hrs. $145.

November 6-8—**Dermatology for the Family Practitioner.** UCD at Del Monte Hyatt House, Monterey. Sunday-Tuesday. 14½ hrs. $100.

November 6-9—**California Academy of Family Physicians—Annual Scientific Assembly.** Masonic Auditorium, San Francisco. Sunday-Wednesday. Contact: CAFP, 9 First St., San Francisco 94105. (415) 982-6091.

November 11-13—**Health Aspects of Human Sexuality.** UCSF Human Sexuality Program. Friday-Sunday. 20 hrs. Contact: Human Sexuality Program, 350 Parnassus, Suite 700, San Francisco 94143. (415) 666-4787.

November 18-20—**Sexual Problems in Medical Practice.** USC at Gene Autry Hotel, Palm Springs. Friday-Sunday.

November 18-22—**Gerontological Society—Annual Scientific Meeting.** Co-sponsored by UCSF. Hilton Hotel, San Francisco. Friday-Tuesday. 25 hrs. Contact: E. Jane White, Gerontological Society, 2728 Durant Ave., Berkeley 94704. (415) 848-7604.

December 1-4—**The Health Professional and Sexuality: An Essential Dimension in Patient Care.** UCD at Hyatt Lake Tahoe, Incline Village. Thursday-Sunday.

December 5-9—**Advances in Diagnosis and Treatment in Clinical Medicine.** See Medicine, December 5-9.

December 9-11—**Clinical Toxicology, Pharmacology and Carcinogenic Hazards.** UC Extension, Berkeley, and UCSF at Hyatt Regency Hotel, San Francisco. Friday-Sunday. 13 hrs. $150. Contact: Medical Symposia, Div. of Letters and Sciences, UC Extension, Berkeley 94720. (415) 642-1061.

December 14—**Treatment of Parkinsonism.** See Surgery, December 14.

January 18-20—**Infectious Disease.** USC. Wednesday-Friday.

January 19-20—**Biofeedback Techniques in Physical Medicine and Rehabilitation.** Herrick Memorial Hospital, Berkeley. Thursday-Friday. Contact: Marie Ham, Med. Staff Sec., Herrick Mem. Hosp., 2001 Dwight Way, Berkeley 94704. (415) 845-0130, ext. 418.

January 19-21—**Medical Aspects of Aging.** UCLA at Sheraton Universal Hotel, No. Hollywood. Thursday-Saturday.

January 21—**Systemic Disease/Eye, Mouth, Skin Manifestations.** Continuing Medical Education/San Luis Obispo Consortium at Hilton Inn, San Luis Obispo. Saturday. 5 hrs. $25 for non-consortium members. Contact: Billy Mounts, MD, Chr., CME/SLO Consortium, P.O. Box 319, San Luis Obispo 93406.

January 23-27—**Therapy: Principles and Use of Drugs.** STAN. Monday-Friday. 27 hrs. $265.

January 27-28—**Nutrition.** UCSF. Friday-Saturday.

January 28-29—**Pediatrics for the Primary Physician: A Practical Update.** UCLA. Saturday-Sunday. 10 hrs. $135.

February 1-4—**Physician and the Hospital.** USC at Canyon Hotel, Palm Springs. Wednesday-Saturday.

February 3-5—**American Medical Association—Regional Meeting.** Sahara Tahoe Hotel, Stateline. Friday-Sunday. Contact: Mr. G. K. Jewett, Dir., Dept. of Cont. Ed. Seminars, AMA, 535 N. Dearborn St., Chicago 60610. (312) 751-6000.

February 8-11—**Primary Care—Current Management of Common Office Problems.** UCSF. Wednesday-Saturday.

February 10-11—**Alcoholism Update—4th National Seminar.** Vista Hill Foundation at Hotel del Coronado, Coronado. Friday-Saturday. 9 hrs. Contact: Virginia Everett, Dir., Public Relations, Vista Hill Foundation, 7798 Starling Dr., San Diego 92123. (714) 278-6761.

February 10-12—**Headaches: Evaluation and Management** UCLA at Beverly Hilton Hotel, Beverly Hills. Friday-Sunday. 18 hrs.

February 12-13—**Workshop on Alcoholism—A Clinical Approach for Health Professionals.** UCSD at Sheraton Inn-Airport, San Diego. Sunday-Monday. 13 hrs.

February 13-17—**LLU Alumni Association—Annual Post graduate Convention.** LLU. Monday-Friday.

February 15-17—**Course for Physicians in Family Practice—27th Annual.** Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Ann Raisbeck, Dept of Med. Ed., Mt. Zion Hospital and Med. Ctr., P. O. Box 7921, San Francisco 94120. (415) 567-6600, ext 2401.

February 20-24—**Caring for Older Persons.** Medical Communications and Services Assn. at Kona Surf Hotel, Kailua Kona, Hawaii. Monday-Friday. 31 hrs. $195. Contact MCSA, 315 University District Bldg., 1107 N. E. 45th St Seattle, WA 98105. (206) 633-0505.

February 27-March 3—**Basic Science for Clinicians.** STAN Monday-Friday. 24½ hrs. $265.

February 27-March 3—**Clinical Management of Sexual Problems.** Medical Communications and Services Assn. at Sheraton Hotel, Molokai, Hawaii. Monday-Friday. 30 hrs. $195 Contact: MCSA, 315 University District Bldg., 1107 N. E 45th St., Seattle, WA 98105. (206) 633-0505.

March 4—**Controversies in Applied Immunotherapy.** UCSF a Children's Hospital, San Francisco. Saturday.

March 4-5—**Genetic Counseling.** UCLA. Saturday-Sunday.

March 6-8—**Diagnosis, Treatment and Prevention of Genetic Disease.** American College of Physicians; Harbor Gen. Hospital; Nat'l Foundation-March of Dimes at Riviera Hotel Palm Springs. Monday-Wednesday. Contact: Registrar, ACP 4200 Pine St., Philadelphia 19104.

March 7-May 23—**Bedside Clinics.** USC at Children's Hospital Los Angeles. Tuesday evenings.

March 8-10—**Neurology for Non-Neurologists.** UCSD at Hilton Hotel, San Diego. Wednesday-Friday. 22 hrs.

March 11-12—**Liaison Psychiatry.** UCLA. Saturday-Sunday 14 hrs.

March 15-18—**Critical Care Medicine.** USC at MGM Grand Hotel, Las Vegas. Wednesday-Saturday.

March 17-22—**California Medical Association—107th Annual Session.** Fairmont Hotel, San Francisco. Friday-Wednesday Contact: Linda Ramsey, CMA.

Audio-Digest Foundation. A nonprofit educational subsidiary of the California Medical Association. Twice-a-month tape recorded summaries of leading national meetings. Service by subscription in: Anesthesiology, Family Practice, Intern

Medicine, Obstetrics/Gynecology, Ophthalmology, Otorhinolaryngology, Pediatrics, Psychiatry, Surgery. ($90.00 per year for 24 one-hour cassettes or reels.) New catalog of lectures and panel discussions in all areas of medical practice also available, as well as cassette album condensations of the following 1977 specialty meetings: postgraduate courses from the annual meeting of the American Psychiatric Assn., workshops from the annual meeting of the American College of Physicians, and postgraduate courses from the annual sessions of the American College of Obstetricians and Gynecologists. For further information on subscriptions, catalogs and special courses, contact Mr. Claron L. Oakley, Editor, 1577 E. Chevy Chase Dr., Glendale 91206.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Physician-in-Residence Preceptorship in Pulmonary Disease. USC, Pulmonary Disease Section, Dept. of Medicine and Postgraduate Medical Education. One month or more, by arrangement. Opportunity for practicing physician to achieve specified knowledge and skills in adult pulmonary medicine. Contact: Oscar J. Balchum, MD, PhD, USC.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Department of Internal Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen R. Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, 97201.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

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ALBERT E. HIRST, MD, Professor of Pathology, Loma Linda University School of Medicine, Loma Linda, California

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DANIEL STEINBERG, MD, PhD, Professor of Medicine, Head, Division of Metabolic Disease, University of California, San Diego School of Medicine, La Jolla, California

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Information

REGISTRATION FEES: Physicians $75.00; Residents, Interns, Registered Nurses and Others $35.00 (includes luncheon, refreshment breaks and exhibits). Make checks payable to: Lyman A. Brewer III Symposium

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Rounds. Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

October 20-21—**Seventeenth Annual Postgraduate Course in Medicine and Surgery.** Providence Hospital, Department of Family Practice, 700 NE 47th, Portland 97213. Contact: Robert Cockburn, MD, 9204 SE Mitchell, Portland 97266.

December 1—**Family Practice Educational Program: Empathetic Understanding.** Main Auditorium, Woodland Park Hospital, Portland. Contact: R. T. Gustafson, MD, 10300 NE Hancock Street, Portland 97220.

INTERNAL MEDICINE

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

November 2-4—**Oregon Medical Association Annual Scientific Session.** Red Lion Motor Inn and Oregon Medical Association Headquarters, Portland. Contact: Sondra Gleason, Oregon Medical Association, 5210 SW Corbett Street, Portland 97201.

November 4-5—**Fourth Annual Critical Care Symposium.** Sheraton Hotel, Portland. Contact: J. S. Reinschmidt, MD, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

November 8—**Oregon Lung Association Sixth Annual Respiratory Disease Conference.** Sacred Heart Hospital, Eugene. Contact: Oregon Lung Association, 1020 SW Taylor, Portland 97205.

December 9-10—**Urology for the Non-Urologist.** Oregon Medical Association Headquarters, Portland. Contact: J. S. Reinschmidt, MD, Director of Continuing Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

December 15—**Current Concepts in Exercise Testing and Training in Coronary Heart Disease.** YMCA, Portland. Contact: M. R. Malinow, MD, 505 NW 185th Avenue, Beaverton 97005.

WASHINGTON, ALASKA, MONTANA AND IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-64, Seattle, Washington 98195. Phone: (206) 543-6995.

October 14-15—**Annual Cancer Conference.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

October 24-25—**Anaerobic Infections, Post-operative Infections, Infections of the Nervous System—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, Oct. 24, Wenatchee; 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, Oct. 25, Yakima, 5-7 p.m., Memorial Hospital. Contact: Harry Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 248-6791.

October 26-28—**Lipid Metabolism in Diabetes—Univ. of Wash. Internal Medicine Review Sessions in Montana.** Wednesday, Oct. 26, Great Falls. Contact: Mr. John Breeden, P.O. Box 2829, Great Falls, MT 59403. (406) 453-1493. Thursday, Oct. 27, Billings; 7:30-10 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, Oct. 28, Missoula; 8:30-11 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

November 16—**New Antibiotics, Surgical Antibiotic Prophylaxis—University of Wash. in Anacortes, Wash.** Wednesday, 8-10 a.m., Island Hospital. Contact: Harry Eiesland, MD, 24th St. and "M" Ave., Anacortes, WA 98221. (206) 293-3101.

November 16-18—**Osteoporosis and Metabolic Bone Disease Scanning—Univ. of Wash. Internal Medicine Review Sessions in Montana.** Wednesday, Nov. 16, Great Falls. Contact: Mr. John Breeden, Box 2829, Great Falls, MT 59403. (406) 453-1493. Thursday, Nov. 17, Billings; 7:30-10 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, Nov. 18, Missoula; 8:30-11 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

November 18—**Disorders of the Low Back.** Friday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

November 28-29—**Pulmonary I—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, Nov. 28, Wenatchee; 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, Nov. 29, Yakima; 5-7 p.m., Memorial Hospital. Contact: Harry Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 248-6791.

December 1-2—**Local Anesthesia and Nerve Blocks for the Office Practice.** Thursday-Friday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101 (206) 223-6898.

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FEBRUARY 25 TO MARCH 4, 1978

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MARCH 4 TO MARCH 11, 1978

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MARCH 4 TO MARCH 11, 1978

VAIL GENERAL SURGERY CONFERENCE
MARCH 11 TO MARCH 18, 1978

VAIL INTERNAL MEDICINE CONFERENCE
MARCH 18 TO MARCH 25, 1978

VAIL UROLOGY CONFERENCE
MARCH 18 TO MARCH 25, 1978

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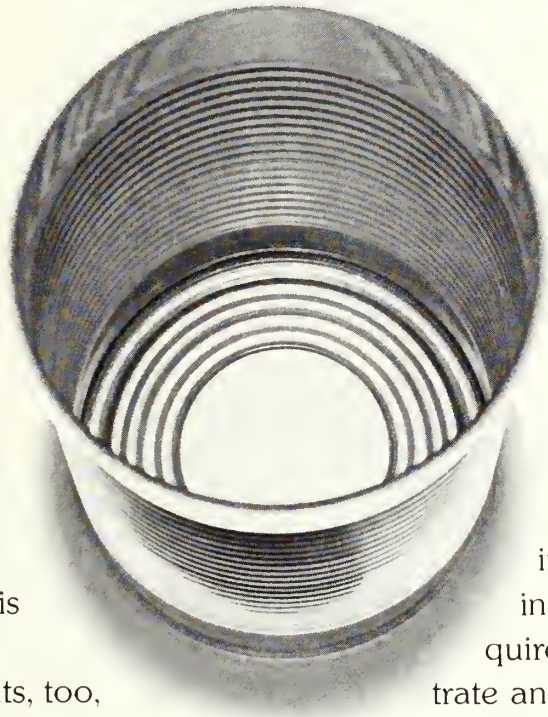

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Warnings: *Usage in Pregnancy:* The safety of the use of Brethine, brand of terbutaline sulfate, in human pregnancy has not been established. The use of the drug in pregnancy, lactation, or women of childbearing potential requires that the expected therapeutic benefit of the drug be weighed against its possible hazards to the mother or child.

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(metolazone) Pennwalt

2½ mg, 5 mg and 10 mg tablets

once-daily antihypertensive diuretic

Recommended initial dosage in mild to moderate essential hypertension–2½ to 5 mg once daily

Before prescribing, see complete prescribing information in the package insert, or in PDR, or available from your Pennwalt representative. The following is a brief summary. **Indications:** Zaroxolyn (metolazone) is an antihypertensive diuretic indicated for the management of mild to moderate essential hypertension as sole therapeutic agent and in the more severe forms of hypertension in conjunction with other antihypertensive agents. Also, edema associated with heart failure and renal disease. **Contraindications:** Anuria, hepatic coma or precoma; allergy or hypersensitivity to Zaroxolyn. Or, as a routine in otherwise healthy pregnant women. **Warnings:** In theory cross-allergy may occur in patients allergic to sulfonamide-derived drugs, thiazides or quinethazone. Hypokalemia may occur, and is a particular hazard in digitalized patients; dangerous or fatal arrhythmias may occur. Azotemia and hyperuricemia may be noted or precipitated. Considerable potentiation may occur when given concurrently with furosemide. When used concurrently with other antihypertensives, the dosage of the other agents should be reduced. Use with potassium-sparing diuretics may cause potassium retention and hyperkalemia. Administration to women of childbearing age requires that potential benefits be weighed against possible hazards to the fetus. Zaroxolyn appears in the breast milk. Not for pediatric use. **Precautions:** Perform periodic examination of serum electrolytes, BUN, uric acid, and glucose. Observe patients for signs of fluid or electrolyte imbalance. These determinations are particularly important when there is excessive vomiting or diarrhea, or when parenteral fluids are administered. Patients treated with diuretics or corticosteroids are susceptible to potassium depletion. Caution should be observed when administering to patients with gout or hyperuricemia or those with severely impaired renal function. Hyperglycemia and glycosuria may occur in latent diabetes. Chloride deficit and hypochloremic alkalosis may occur. Orthostatic hypotension may occur. Dilutional hyponatremia may occur in edematous patients in hot weather. **Adverse Reactions:** Constipation, nausea, vomiting, anorexia, diarrhea, bloating, epigastric distress, intrahepatic cholestatic jaundice, hepatitis, syncope, dizziness, drowsiness, vertigo, headache, orthostatic hypotension, excessive volume depletion, hemoconcentration, venous thrombosis, palpitation, chest pain, leukopenia, urticaria, other skin rashes, dryness of mouth, hypokalemia, hyponatremia, hypochloremia, hypochloremic alkalosis, hyperuricemia, hyperglycemia, glycosuria, raised BUN or creatinine, fatigue, muscle cramps or spasm, weakness, restlessness, chills, and acute gouty attacks. **Usual Initial Once-Daily Dosages:** mild to moderate essential hypertension—2½ to 5 mg; edema of cardiac failure—5 to 10 mg, edema of renal disease—5 to 20 mg. Dosage adjustment may be necessary during the course of therapy. **How Supplied:** Tablets, 2½, 5 and 10 mg.

References:

1. Dornfeld L, Kane R. Metolazone in essential hypertension: The long-term clinical efficacy of a new diuretic. *Curr Ther Res* **18** 527-533, 1975
2. Cangiano JL: Effects of prolonged administration of metolazone in the treatment of essential hypertension. *Curr Ther Res* **20** 745-750, 1976.
3. Data on file: Medical Department, Pennwalt Prescription Products.

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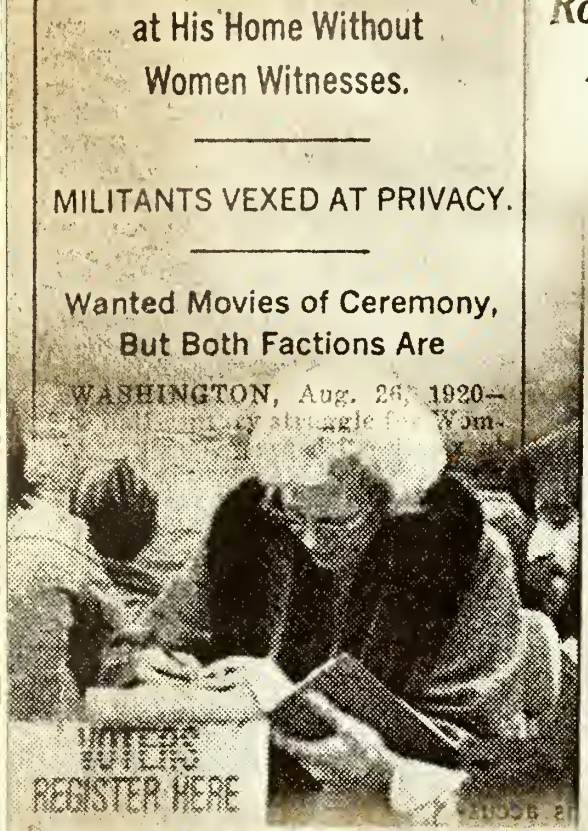
WASHINGTON, Aug. 26, 1920—



Social Security Bill Is Signed Gives Pensions to Aged, Jol

Roosevelt Approves Message Intended to Benefit 30,0 Persons When States Adopt Cooperating Laws-He C the Measure 'Cornerstone' of His Economic Progr

WASHINGTON, Aug. 4, The Social Security Bill, ro a broad program of unem lo insurance and old age pe and counted upon to be fi 20,000,000 persons, becam l day when it was signed y dent Roosevelt in the p se those chiefly responsibl fo ting it through Congres

Mr. Roosevelt call th me "the cornerstone in a tr which is being b th me s comple ri to

SENATE APPROVES 18-YEAR OLD VOTE IN ALL ELECTIONS

Amendment to Constitution is Sent to House, Where Passage is Expected

WASHINGTON, March 10, 1971—The Senate approved today, 94 to 0, and sent to

TRUMAN CLOSES ITED NATIONS CONFEREN VITH PLEA TO TRANSLATE CHARTER INTO DEEDS

NEW WORLD HOPE

President Hails 'Great Instrument of Peace,' Insists It Be Used

HISTORIC LANDMARK

Meeting Gives Standing Ovation as Executive Pictures Peace Gain

"If we fail to use it," he declared to the solemn final meeting of the delegates, 'we shall betray all of those who have died in order that we might meet here in freedom and safety to create it.'

"If we seek to use it selfishly—for the advantage of any one nation or any small group of nations—we shall be equally guilty of that betrayal."

Fervent Interpolation

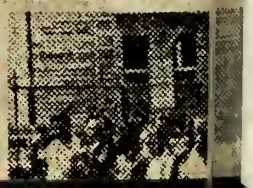
The President, speaking in the auditorium of the War Memorial Opera House, built in memory of sons of the Golden Gate city who gave their lives in the first World War, in which he himself served, seemed to give unconscious expression to the solemn feeling of the occasion when, at the outset of his speech, he interpolated the words, half a hope, half a prayer:

"Oh, what a great day this can be in history!"

Just before the plenary session

JOL SIGNI the Draf Ends No

WASHINGTON, Jan. 27, 1973—"With the signing of the peace agreement in Paris today, and after receiving a report from the Secretary of the Army that



PATIENT PACKAGE INSERTS: A CONCEPT WHOSE TIME HAS COME?

The consumer's right to know is an irreversible and desirable trend of the Seventies. It extends, and properly, to a patient's right to know more about his or her prescription medications. One way, gaining favor, is through patient package inserts. Wisely-prepared and properly distributed when medically indicated, they could markedly improve patient knowledge and drug therapy—laudable goals by anyone's standards.

The PMA endorses these goals and will work with government, the health professions and consumers to achieve them.

The Advantages

The concept holds promise of benefits: better patient understanding of the product prescribed, better adherence to the treatment plan, and more awareness of possible side reactions.

Every doctor has had patients who fail to finish antibiotic regimens because they feel better. Some patients assume that if one tranquilizer or analgesic is good, two may be twice as good. Still others fail to report dizziness while on antihypertensive therapy —and so on.

Problems like these might arise less often if the patient received written information in addition to verbal instructions. Some studies suggest that patients are more receptive to such materials, and they more often understand the verbal instructions and follow them, when inserts are used.

The Disadvantages

There are also some potential problems. Obviously, the inserts must be clearly phrased, without extraneous or complex detail. How much information is enough? How can it be kept current? Should all patients receive the same information? Should inserts be included with all drugs? Should only potential problems be listed or are patients better off with a "fair balance" presentation that describes usefulness as well as drawbacks?

These and similar questions require answers, since model inserts have yet to be properly developed and tested. Despite the need for these studies, the FDA is proceeding prematurely with inserts on selected products. We think the Congress is the only place where the matter can be given the proper legal status and direction, particularly since it represents a conceptual change in the legal, medical and social framework of the nation's prescription drug information system.

The Solution

The PMA believes that carefully-devised pilot studies of various kinds of inserts are needed. They should be developed and implemented with full participation by doctors, pharmacists, consumers, communications experts and the drug industry. Such studies will provide reliable pathways to follow, so that inserts will be useful aids to medical practice.

And particularly we think that you should be closely involved in this debate and in these studies and decisions. Otherwise, people with less experience and qualifications may control the purposes, content and use of a tool with considerable promise for improved patient care. It could make a difference in your practice tomorrow, and more importantly, in the health of your patients.

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- **DORCOL® PEDIATRIC COUGH SYRUP:** Full-teaspoon pediatric dosage for cough and nasal congestion, without narcotics or antihistamines.

The Recommendables™ line does not contain FD&C yellow #5 (tartrazine dye).

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Tablets

Percodan® (II)

DESCRIPTION Each yellow, scored tablet contains 4.50 mg oxycodone HCl (WARNING May be habit forming), 0.38 mg oxycodone terephthalate (WARNING May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine.

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCODAN®, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCODAN® is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCODAN® should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCODAN® may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCODAN® should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCODAN® should not be administered to children.

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCODAN® or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCODAN® should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCODAN® may be additive with that of other CNS depressants. See WARNINGS.

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Manati, Puerto Rico 00701
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November 1977 EDO 149P

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What is causing pain? How is it perceived by you and your patient?

2. Prescribe a rapid-acting agent

Select a readily-absorbed oral agent that usually acts within 15 to 30 minutes.

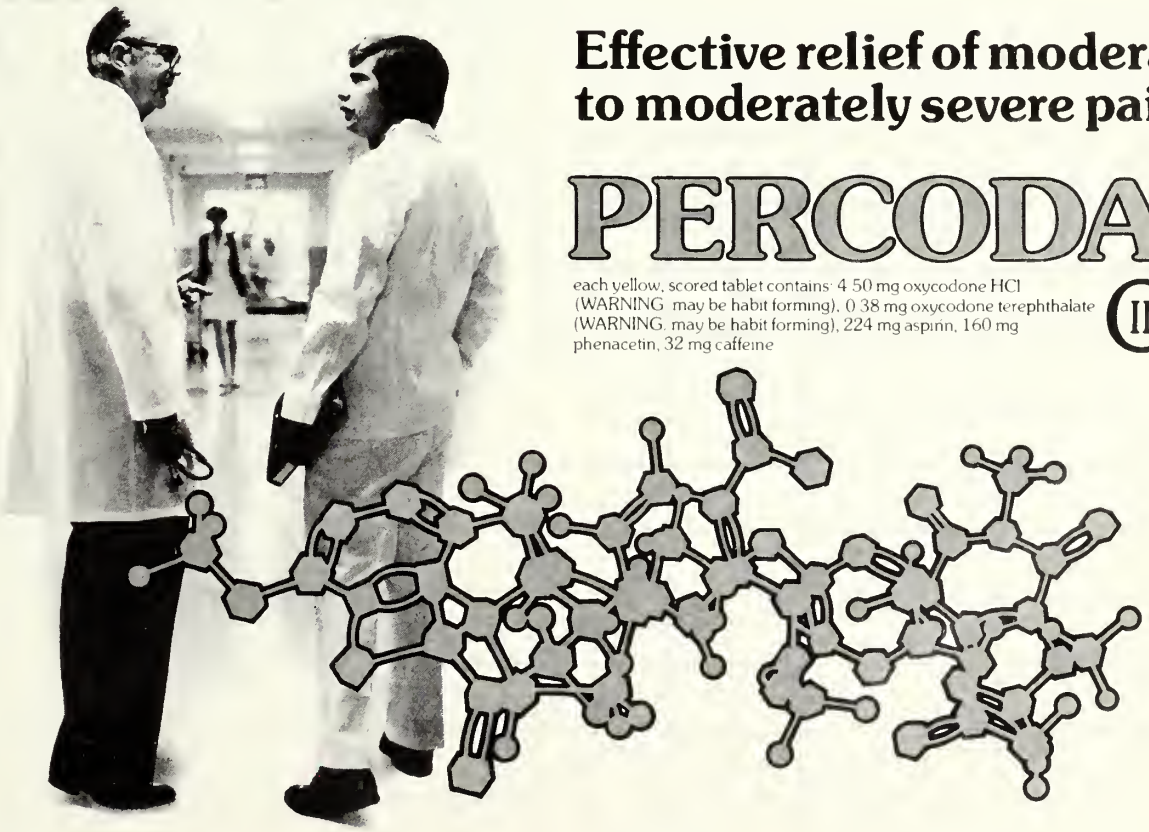
3. Minimize potential risk

Prescribe in limited quantities for selected patients.

Schedule II classification means no refills, no telephone Rx. Patients with persistent pain must return for your evaluation of analgesic needs.

4. Provide adequate analgesia with minimum doses

Consider PERCODAN® because patients rarely ask for increased dosage. PERCODAN® relief can last up to six hours–until time for next tablet.



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Tablets

PERCODAN®

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Pectin	142.8 mg.
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- Enhances output of less viscid secretions to aid in the removal of inspissated mucus.
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- Reduces severity, frequency and patient awareness of cough.
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*National Disease & Therapeutic Index, Jan.-Dec., 1976. IMS America Ltd., Ambler, Pa. 1976.
†Amer. Med. Assn., Dept. of Drugs, A.M.A. Drug Evaluations, 2nd Edition, Publishing Sciences Group, Inc., Acton, Mass., 1973, pp. 482-3

Robitussin®-DAC—Each 5 ml (1 teaspoonful) contains: Guaifenesin, NF 100 mg; Pseudoephedrine Hydrochloride, NF 30 mg; Codeine Phosphate, USP 10 mg (Warning: May be habit forming) in a palatable, aromatic syrup. Alcohol, 1.4 per cent. INDICATIONS: For the temporary relief of cough and nasal congestion as may occur with the common cold or with inhaled irritants. CONTRAINDICATIONS: Hypersensitivity to any of the ingredients, marked hypertension, hyperthyroidism, or in patients who are receiving MAO inhibitors or antihypertensive medication. WARNINGS: Use this product with caution in children under 2 years or in children taking another drug. Prescribe cautiously for patients with persistent or chronic cough such as comes with smoking, asthma, emphysema, or where cough is accompanied by excessive secretions. Caution should be taken in administering this drug to patients with high blood pressure, heart disease or diabetes. In patients with chronic pulmonary disease or shortness of breath, this product should be administered with caution. As with all products containing sympathomimetic amines, use with caution in patients with prostatic hypertrophy or glaucoma. Do not exceed recommended dosage because at higher doses nervousness, dizziness or sleeplessness may occur. May cause or aggravate constipation. NOTE: Guaifenesin has been shown to produce a color interference with certain clinical laboratory determinations of 5-hydroxyindoleacetic acid (5-HIAA) and vanillylmandelic acid (VMA). ADVERSE REACTIONS: Agitation, dizziness, insomnia, palpitations or nausea may occur. In such instances, reduction in frequency and/or quantity of dose is indicated. RECOMMENDED DOSAGE: Adults: 1 or 2 teaspoonfuls every four hours, not to exceed 12 teaspoonfuls in a 24-hour period; children 6 to under 12 years: 1 teaspoonful every four hours, not to exceed 6 teaspoonfuls in a 24-hour period; children under 2 years: use as directed by a physician. ALSO AVAILABLE: Robitussin® Robitussin A-C® Robitussin with codeine Robitussin-CF® Robitussin with phenylpropanolamine and dextromethorphan. Robitussin-DM® Robitussin with dextromethorphan Cough Calmers® lozenges (Robitussin-PE®—Robitussin with pseudoephedrine) Robitussin DM in solid form. A. H. Robins Co., Richmond, Va. 23220

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the compatible vasodilator TABLETS, 20 mg.

***Indications:** Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency.
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.

Final classification of the less-than-effective indications requires further investigation.

Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg. Vasodilan injection, isoxsuprine HCl, 5 mg., per ml.

Dosage and Administration: Oral: 10 to 20 mg., three or four times daily. Intramuscular: 5 to 10 mg. (1 or 2 ml.) two or three times daily. Intramuscular administration may be used initially in severe or acute conditions.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

Parenteral administration is not recommended in the presence of hypotension or tachycardia.

Intravenous administration should not be given because of increased likelihood of side effects.

Adverse Reactions: On rare occasions oral administration of the drug has been associated in time with the occurrence of hypotension, tachycardia, nausea, vomiting, dizziness, abdominal distress, and severe rash. If rash appears the drug should be discontinued.

Although available evidence suggests a temporal association of these reactions with isoxsuprine, a causal relationship can be neither confirmed nor refuted.

Administration of single dose of 10 mg. intramuscularly may result in hypotension and tachycardia. These symptoms are more pronounced in higher doses. For these reasons single intramuscular doses exceeding 10 mg. are not recommended. Repeated administration of 5 to 10 mg. intramuscularly at suitable intervals may be employed.

Supplied: Tablets, 10 mg., bottles of 100, 1000, 5000 and Unit Dose; Tablets, 20 mg., bottles of 100, 500, 1000, 5000 and Unit Dose; Injection, 10 mg. per 2 ml. ampul, box of six 2 ml. ampuls. U.S. Pat. No. 3,056,836

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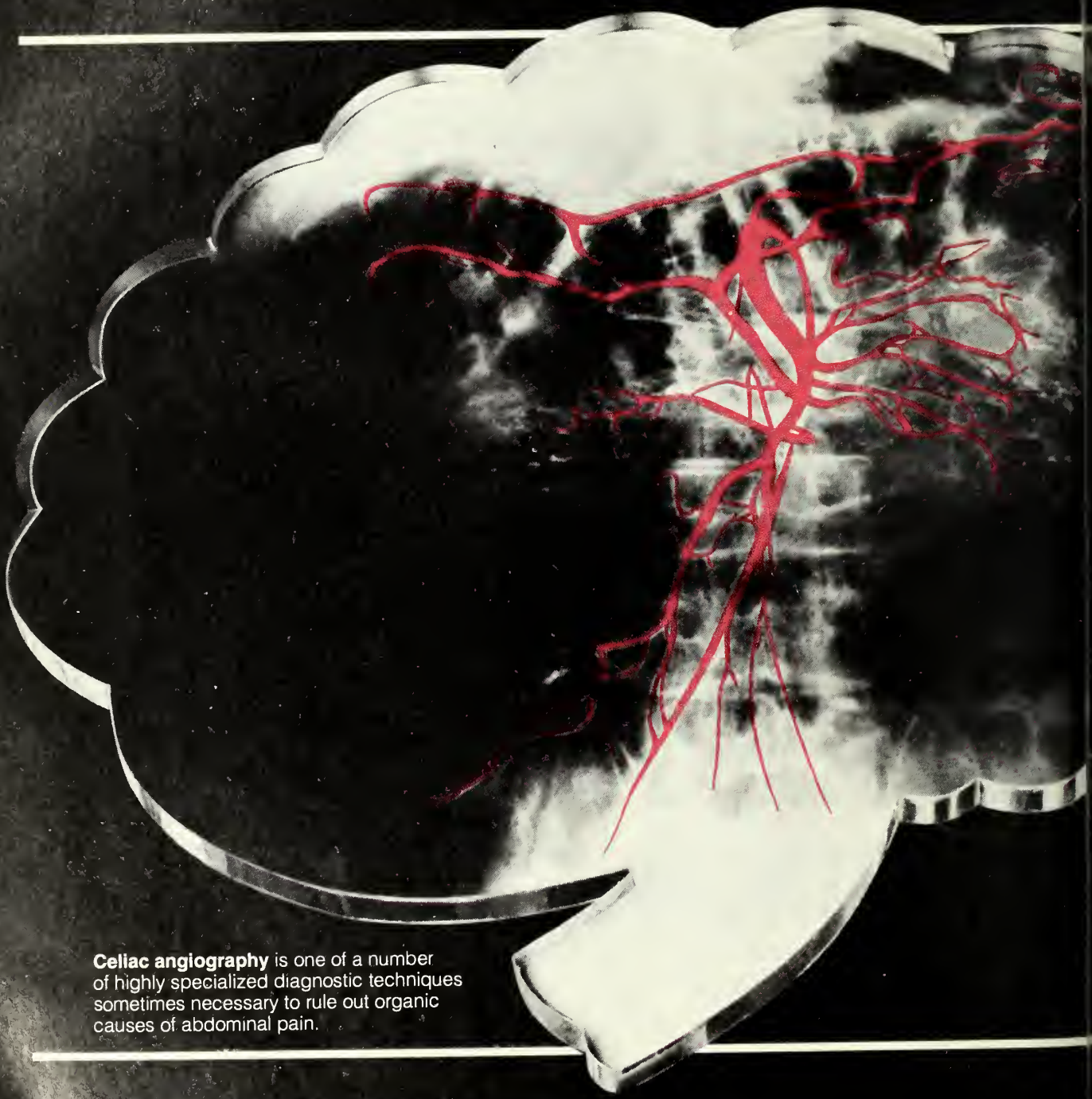

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A clear treatment advantage for patients with irritable bowel syndrome

ROCHE

*This drug has been evaluated as possibly effective for this indication. Please see following page for brief summary of prescribing information.

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* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Patients with glaucoma; prostatic hypertrophy and benign bladder neck obstruction; known hypersensitivity to chlordiazepoxide hydrochloride and/or clidinium bromide.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering Librium® (chlordiazepoxide hydrochloride) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergic drugs, an inhibiting effect on lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude development of ataxia, oversedation or confusion (not more than two capsules per day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacologic effects of agents, particularly potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: No side effects or manifestations not seen with either compound alone have been reported with Librax. When chlordiazepoxide hydrochloride is used alone, drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are avoidable in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally with chlordiazepoxide hydrochloride, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax are typical of anticholinergic agents, *i.e.*, dryness of the mouth, blurring of vision, urinary hesitancy and constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

Dosage: Individualize for maximum beneficial effects. Usual maintenance dose is 1 or 2 capsules, 3 or 4 times a day, before meals and at bedtime. Geriatric patients—see Precautions.

How Supplied: Librax is available in green capsules, each containing 5 mg chlordiazepoxide hydrochloride (Librium®) and 2.5 mg clidinium bromide (Quarzan®)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50, available singly and in trays of 10.

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Average weight loss of 2.15 lbs per week compared in clinical studies against a placebo.

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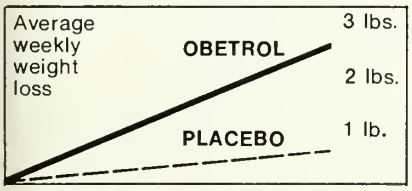

Obetrol eases the discomfort of adherence to a restricted diet in individuals who are well motivated to reduce their food intake.

Clinical studies disclose amphetamines to be the most dependable drug in a weight-reduction regimen compared to other anorexigenic agents.

Amphetamines have a significant potential for abuse. In view of their limited short-term anorectic effect and rapid development of tolerance, they should be used with extreme caution and only for limited periods of time in weight reduction programs.

Actions: Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. The anorectic effect diminishes after a few weeks.

Indications: Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.

Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.

Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.

Dosage and Administration: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.

1. Narcolepsy: Usual dose 5 to 60 milligrams per day in divided doses.
2. Minimal brain dysfunction:
   a. Not recommended for children under 3 years of age.
   b. Children from 3 to 5 years of age: 2.5 milligrams daily, raised in increments of 2.5 milligrams at weekly intervals until optimal response is obtained.
   c. Children 6 years of age and older, 5 milligrams, once or twice daily, increased in increments of 5 milligrams at weekly intervals. Only in rare cases will it be necessary to exceed a total of 40 milligrams per day.
3. Obesity: Usual adult dose 5 to 30 milligrams per day in divided doses.

Overdosage: Manifestations of acute overdosage with amphetamines include restlessness, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.

Management of acute amphetamine intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard.

Availability: Supplied in bottles of 100; 500 and 1,000 tablets.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

January 1973

Comprehensive informational brochure available upon written request. Prescribe Obetrol for appetite control.

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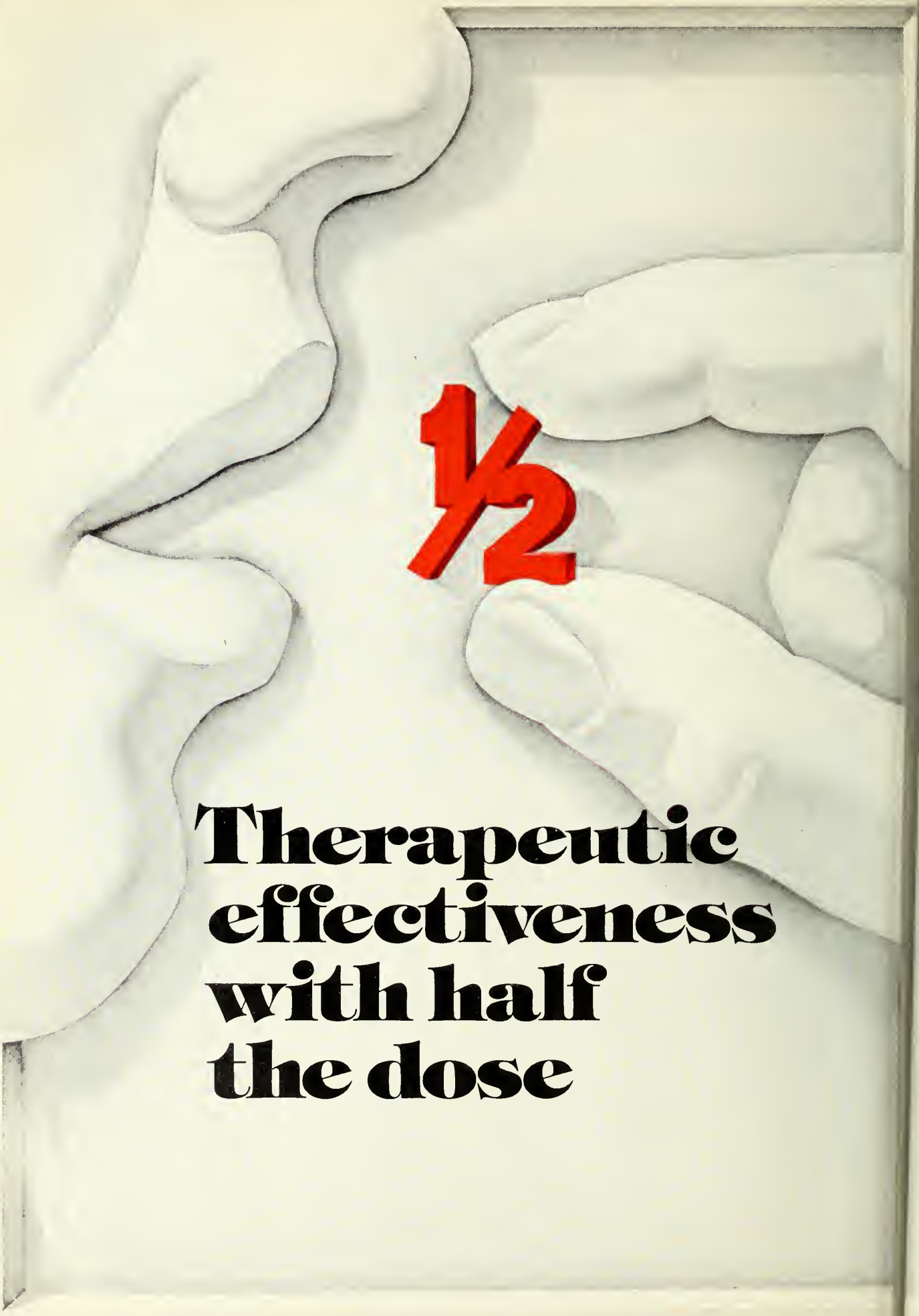
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**Based on list-price comparison.

See Clinical Considerations section on following page.

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Fulvicin® P/G

griseofulvin [ultramicrosize], USP

(specially processed) **125 mg. tablets**

Clinical Considerations: INDICATIONS FULVICIN P/G Tablets are indicated for the treatment of ringworm infections of the skin, hair, and nails, namely tinea corporis, tinea pedis, tinea cruris, tinea barbae, tinea capitis, tinea unguium (onychomycosis) when caused by one or more of the following genera of fungi: *Trichophyton rubrum, Trichophyton tonsurans, Trichophyton mentagrophytes, Trichophyton interdigitalis, Trichophyton verrucosum, Trichophyton megnini, Trichophyton gallinae, Trichophyton crateriformi, Trichophyton sulphureum, Trichophyton schoenleini, Microsporum audouini, Microsporum canis, Microsporum gypseum,* and *Epidermophyton floccosum*

Note Prior to therapy, the type of fungi responsible for the infection should be identified

The use of this drug is not justified in minor or trivial infections which will respond to topical agents alone

Griseofulvin is not effective in the following Bacterial infections, Candidiasis (Moniliasis), Histoplasmosis, Actinomycosis, Sporotrichosis, Chromoblastomycosis, Coccidioidomycosis, North American Blastomycosis, Cryptococcosis (Torulosis), Tinea versicolor, and Nocardiosis

CONTRAINDICATIONS This drug is contraindicated in patients with porphyria, hepatocellular failure, and in individuals with a history of hypersensitivity to griseofulvin

WARNINGS *Prophylactic Usage* Safety and efficacy of griseofulvin for prophylaxis of fungal infections have not been established.

Animal Toxicology Chronic feeding of griseofulvin, at levels ranging from 0.5-2.5% of the diet, resulted in the development of liver tumors in several strains of mice, particularly in males. Smaller particle sizes result in an enhanced effect Lower oral dosage levels have not been tested Subcutaneous administration of relatively small doses of griseofulvin once a week during the first three weeks of life has also been reported to induce hepatomata in mice Although studies in other animal species have not yielded evidence of tumorogenicity, these studies were not of adequate design to form a basis for conclusions in this regard

In subacute toxicity studies, orally administered griseofulvin produced hepatocellular necrosis in mice, but this has not been seen in other species. Disturbances in porphyrin metabolism have been reported in griseofulvin-treated laboratory animals. Griseofulvin has been reported to have a colchicine-like effect on mitosis and cocarcinogenicity with methylcholanthrene in cutaneous tumor induction in laboratory animals.

Usage in Pregnancy The safety of this drug during pregnancy has not been established

Animal Reproduction Studies It has been reported in the literature that griseofulvin was found to be embryotoxic and teratogenic on oral administration to pregnant rats Pups with abnormalities have been reported in the litters of a few bitches treated with griseofulvin. Additional animal reproduction studies are in progress

Suppression of spermatogenesis has been reported to occur in rats, but investigation in man failed to confirm this.

PRECAUTIONS Patients on prolonged therapy with any potent medication should be under close observation Periodic monitoring of organ system function, including renal, hepatic, and hematopoietic, should be done

Since griseofulvin is derived from species of penicillin, the possibility of cross sensitivity with penicillin exists, however, known penicillin-sensitive patients have been treated without difficulty

Since a photosensitivity reaction is occasionally associated with griseofulvin therapy, patients should be warned to avoid exposure to intense natural or artificial sunlight Should a photosensitivity reaction occur, lupus erythematosus may be aggravated

Griseofulvin decreases the activity of warfarin-type anticoagulants so that patients receiving these drugs concomitantly may require dosage adjustment of the anticoagulant during and after griseofulvin therapy

Barbiturates usually depress griseofulvin activity, and concomitant administration may require a dosage adjustment of the antifungal agent

ADVERSE REACTIONS When adverse reactions occur, they are most commonly of the hypersensitivity type, such as skin rashes, urticaria, and rarely, angioneurotic edema, and may necessitate withdrawal of therapy and appropriate countermeasures. Paresthesias of the hands and feet have been reported rarely after extended therapy Other side effects reported occasionally are oral thrush, nausea, vomiting, epigastric distress, diarrhea, headache, fatigue, dizziness, insomnia, mental confusion, and impairment of performance of routine activities.

Proteinuria and leukopenia have been reported rarely Administration of the drug should be discontinued if granulocytopenia occurs

When rare, serious reactions occur with griseofulvin, they are usually associated with high dosages, long periods of therapy, or both

1070-5231 JANUARY 1977

For more complete details, consult package insert or Schering literature available from your Schering Representative or Professional Services Department, Schering Corporation, Kenilworth, New Jersey 07033.

Remember to write the "P/G"

BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ANGINA PECTORIS—Edited by Desmond G. Julian, MD, FRCP, British Heart Foundation Professor of Cardiology, University of Newcastle upon Tyne. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1977. 272 pages, $25.00.

HEALTH AND MEDICAL ECONOMICS—A Guide to Information Sources—Volume 7 in the Economics Information Guide Series—Ted J. Ackroyd, Assistant Professor of Health Planning and Administration, College of Human Development, Pennsylvania State University. Gale Research Company, Book Tower, Detroit (48226), 1977. 149 pages, $18.00.

KAREN ANN—The Quinlans Tell Their Story—Joseph and Julia Quinlan with Phyllis Battelle. Doubleday & Company, Inc., Garden City, NY, 1977. 343 pages, $10.00.

MALIGNANT MELANOMA OF THE SKIN AND MUCOUS MEMBRANE—G. W. Milton, MBBS(Adel), FRCS, FRACS, Professor of Surgery, University of Sydney, Director of the Melanoma Unit, Sydney Hospital, Honorary Surgeon, Sydney Hospital; Visiting Professor in Surgery, Liverpool District Hospital; With chapters by V. J. McGovern, MD(NZ), FRACP, FRCPath, FRCPA, Director, Fairfax Institute of Pathology, Royal Prince Alfred Hospital; Lecturer in Pathology, University of Sydney; and Martin G. Lewis, MD, MRC Path(London), Director, Cancer Research Unit, McIntyre Medical Sciences Building, Montreal, with the assistance of Geoffrey Rowden and Terrence M. Phillips, McGill University Cancer Research Unit, McIntyre Medical Sciences Building, Montreal. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1977. 174 pages, $29.00.

MANUAL FOR DISASTER RELIEF WORK—Muriel Skeet, Chief Nursing Officer, British Red Cross Society; Chief Nursing Officer, Joint Committee (Order of St. John of Jerusalem and British Red Cross); Chairman, Advisory Committee, League of Red Cross Societies; President and Chairman, Commonwealth Nurses' Federation; Operational Research Consultant, World Health Organisation and International Hospital Federation. Churchill Livingstone—Medical Division of Longman Inc., 19 W. 44th St., New York City (10036), 1977. 412 pages, $24.50.

THE NEWBORN CHILD—Fourth Edition—David G. Vulliamy, MD, FRCP, DCH, Consultant Paediatrician to the West Dorset District Hospitals. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1977. 223 pages, $7.50 (Paperback).

NOTHING TO FEAR—Coping with Phobias—Fraser Kent. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1977. 216 pages, $7.95.

PIAGETIAN THEORY AND ITS IMPLICATIONS FOR THE HELPING PROFESSIONS: Emphasis—The Handicapped Child—Proceedings Sixth Interdisciplinary Conference: Co-sponsored by University Affiliated Program, Childrens Hospital of Los Angeles and the University of Southern California School of Education. USC Special Order Department & Bookstore, University of Southern California, University Park, Los Angeles (90007), 1977. 462 pages, $10.00 (Paperback).

RECENT ADVANCES IN OBSTETRICS AND GYNAECOLOGY—Number Twelve—Edited by Sir John Stallworthy, MA, Hon DSc (Leeds & Otago), FRCS, FRCOG, Hon FRCSI, Hon FCOG(SA), Hon FACS, Hon FACOG, Emeritus Nuffield Professor of Obstetrics and Gynaecology, University of Oxford; Consultant Obstetric Surgeon, Royal Prince Alfred Hospital, Sydney; Honorary Associate, National Maternity Hospital, Dublin; and Gordon Bourne, FRCS, FRCOG, Consultant in Charge, Department of Obstetrics and Gynaecology, St Bartholomew's Hospital, London; Consultant Gynaecologist, Royal Masonic Hospital, London. Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th Street, New York City (10036), 1977. 368 pages, $27.50.

RECENT ADVANCES IN SURGERY—Number 9—Edited by Selwyn Taylor, DM, MCh, FRCS, Senior Lecturer and Consultant Surgeon, Royal Postgraduate Medical School, Hammersmith Hospital, London. Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th Street, New York City (10036), 1977. 450 pages, $26.50.

REVIEW OF MEDICAL PHYSIOLOGY—Eighth Edition—William F. Ganong, MD, Professor and Chairman, Department of Physiology, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1977. 600 pages, $12.50.

REVIEW OF PHYSIOLOGICAL CHEMISTRY—Sixteenth Edition—Harold A. Harper, PhD, Professor of Biochemistry, University of California, San Francisco; Biochemist Consultant to the Clinical Investigation Center, Naval Regional Medical Center, Oakland; Victor W. Rodwell, PhD, Professor of Biochemistry, Purdue University; Peter A. Mayes, PhD, DSc, Reader in Biochemistry, Royal Veterinary College, University of London; and Associate Authors. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1977. 681 pages, $13.00.

ULTRASONICS IN CLINICAL DIAGNOSIS—Second Edition—Edited by P. N. T. Wells, PhD, F Inst P, Chief Physicist, Avon Area Health Authority (Teaching). Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1977. 195 pages, $18.50.

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THE WESTERN
Journal of Medicine

Refer to: Midgley RC, Cantor D: Upper gastrointestinal hemorrhage—Diagnosis and management. West J Med 127: 371-377, Nov 1977

Upper Gastrointestinal Hemorrhage—Diagnosis and Management

ROBERT C. MIDGLEY, MD, *and* DAVID CANTOR, MD, *Sacramento*

The current management of a patient with upper gastrointestinal hemorrhage involves three steps: initial correction of unstable hemodynamics, obtaining the specific diagnosis of the lesion responsible for gastrointestinal blood loss, and therapy directed at the specific bleeding lesion. The current approach to upper gastrointestinal hemorrhage is carrying out upper gastrointestinal endoscopy following stabilization of the patient. Although improved morbidity and mortality statistics have been slow to appear, the use of endoscopy permits appropriate therapy directed at the specific lesion. Specific therapeutic measures have been outlined for seven common causes of upper gastrointestinal hemorrhage. The advent of therapeutic endoscopy promises to bring further advances in therapy in the near future.

ACUTE UPPER GASTROINTESTINAL HEMORRHAGE is a subject which should be periodically reviewed by all physicians treating patients with this disorder. Although the overall mortality has remained fairly stable at 8 to 10 percent over the last 25 years according to various studies,[1-3] the methods of diagnosis and treatment have been changing rapidly. This article will review some of the concepts necessary for the current management of a patient with acute upper gastrointestinal hemorrhage. The topic will be discussed in the order that the patient is seen; that is, initial management of the patient before the specific diagnosis is known, methods for obtaining a specific diagnosis, and therapy directed at the specific diagnosis.

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Initial Management

The immediate resuscitation of a patient who has bled from his gastrointestinal tract demands precedence over all else. If the initial blood pressure is below 100 mm of mercury systolic or pulse above 120 beats per minute, about 20 percent volume depletion has occurred. In such a patient a large bore intravenous catheter should be placed with immediate administration of fluid, plasma or volume expanders (or both) before the remainder of the evaluation is undertaken.

In the initial workup of the patient a pertinent history, physical examination and initial laboratory data should be obtained in a short time. Important points in the history of a patient with gastrointestinal blood loss is the presence or absence of emesis, its approximate quantity and type —this is, clear versus coffee ground versus bright red blood. Melena is indicative of passage of blood through the digestive tract. But, as transit

time of blood in the digestive tract will vary, the absence of melena does not necessarily exclude a major gastrointestinal hemorrhage. The history of initial vomiting of nonbloody emesis followed by hematemesis is especially suggestive of the Mallory-Weiss syndrome. Orthostatic dizziness or syncope is indicative that severe volume depletion has occurred. The patient should always be questioned about alcohol consumption. The history of ingestion of salicylates is extremely important to elicit, in that gastric erosions induced by salicylates can bleed massively. It is important to elicit the past history of peptic ulcer disease because recurrent ulceration is common. It is important to remember, however, that in patients with a known upper gastrointestinal lesion, the acute bleeding episode will be from a different source than the known lesion in 40 percent of these patients,[2] therefore limiting the amount of useful information obtainable by history alone.

A pertinent physical examination can be carried out quickly. Blood pressure and pulse taken with the patient supine, combined with sitting or standing values, can give important information about the intravascular volume status of the patient. The absence of orthostatic changes usually signifies that a massive hemorrhage has not occurred. The presence of signs of chronic liver disease are readily available on physical examination. Abdominal surgical scars are clues that may indicate a previous operation for peptic ulcer or previous portacaval shunt surgical procedures. Rectal examination or a stool specimen study is important. Nasogastric aspiration, preferably with a large bore Ewald tube, gives much information about the present status of bleeding. The mere passage of the nasogastric tube can produce positive hematest examinations of gastric aspirate. A clear nasogastric aspirate speaks against gastrointestinal hemorrhage above the pylorus although the stomach may be free of blood if bleeding has ceased two to three hours previously. Coffee ground appearing nasogastric aspirate or dark blood aspirated from the stomach signifies that upper gastrointestinal bleeding has occurred and this implies the presence of acid hematin, that is, hemoglobin modified by hydrochloric acid. If this initial coffee ground or dark red aspirate clears after saline or water lavage then this is good evidence that active bleeding has ceased. If there is a persistent pinkish tinge to the nasogastric aspirate after repeated lavage then active hemorrhage persists.

Initial laboratory data will give much information in upper gastrointestinal bleeding. The hematocrit and hemoglobin determinations are more an indicator of the duration of gastrointestinal hemorrhage rather than providing information as to the amount of acute blood loss. Just as the patient can exsanguinate with no blood or melanotic stool in the rectum, so can the patient exsanguinate with a normal hematocrit and hemoglobin. It takes from 12 to 36 hours for the hematocrit and hemoglobin values to drop in acute gastrointestinal hemorrhage. These values are important in assessing the relative amounts of initial packed red cell replacement necessary. The blood urea nitrogen (BUN) level is more an indicator of the volume of blood loss than the hemoglobin. If in a patient with no previous history of renal disease there is a BUN level of above 40 mg per 100 ml, then there is a good likelihood that the patient has had a significant upper gastrointestinal hemorrhage.[4] The BUN is elevated for two reasons. First, the blood in the upper gastrointestinal tract is partially digested and blood proteins are absorbed. Second, the volume depletion produces a prerenal azotemia with consequent elevation of blood urea nitrogen. A serum creatinine determination with the specimen drawn simultaneously with that for the blood urea nitrogen study will rule out significant renal disease as a contributing factor. The prothrombin time is important mainly in alcoholic patients, for abnormal prothrombin time causing a coagulopathy may have to be corrected before control of hemorrhage can be obtained. Estimation of platelets or peripheral smear of blood should be done routinely in that thrombocytopenia associated with chronic liver disease is common. Arterial blood pH should be drawn initially in patients with evidence of massive blood loss in that lactic acidemia can occur due to severe tissue hypoxia seen with massive volume and oxygen carrying capacity depletion present in gastrointestinal hemorrhage. An electrocardiogram should be done. The incidence of silent myocardial infarction in association with gastrointestinal hemorrhage and volume depletion is significant and is an association that can easily be overlooked. The management of the patient will obviously vary if signs of myocardial ischemia are present. Total bilirubin and serum glutamic oxaloacetic transaminase (SGOT) are indicators of acute or chronic liver disease, and the amylase value is helpful in screening for pancreatitis associated with upper

TABLE 1.—*Categories of Upper Gastrointestinal Hemorrhage*

Nonbleeder	
Normal Hct/Hgb	
Negative N/G aspirate	
No orthostatic BP, P changes	
Guaiac negative stools	
Chronic Bleeder	
Normal or decreased Hct/Hgb	
Clear N/G aspirate, guaiac negative or positive	
No orthostatic BP, P changes	
Guaiac positive stools	
Acute, Nonmassive Bleeder	
Normal Hct/Hgb	
Coffee ground N/G aspirate, clears with lavage	
No orthostatic BP, P changes	
Guaiac positive or negative stools	
Acute, Massive Bleeder	
Normal or decreased Hct/Hgb	
N/G aspirate; bright red blood, does not fully clear with lavage	
Orthostatic BP, P changes	
Guaiac positive or negative stools	
(See text for further explanation)	
Hct = hematocrit	BP = blood pressure
Hgb = hemoglobin	P = pulse
N/G = nasogastric	

gastrointestinal hemorrhage. Of course, blood for type and crossmatch should be drawn with the initial laboratory work in all cases where significant hemorrhage is being considered. Serum alcohol or salicylate level determination may be helpful in unreliable patients.

Following the above evaluation, the physician treating a patient with gastrointestinal hemorrhage can often categorize the type of bleeding (Table 1). The *nonbleeder* is a patient who may have had dark emesis and suspected blood loss, who may be malingering, or who may have ingested beets and noticed dark stools, or may have ingested iron or bismuth and noted black stools. In these patients there are normal hematocrit and hemoglobin values, the nasogastric aspirate does not contain blood, there are no orthostatic changes, and the stools are guaiac negative. This patient can be easily managed with reassurance. If there is any doubt whether the patient belongs in this category the patient should be observed, worked-up appropriately and assigned a new category if the diagnosis remains in doubt.

The *chronic bleeder* is a patient who is losing blood through the gastrointestinal tract but is not acutely volume depleted. The patient may have normal or decreased hematocrit and hemoglobin values, he will have clear nasogastric aspirate which may be either guaiac negative or positive, he has no orthostatic blood pressure or pulse changes, and guaiac positive stools are present. This patient deserves thorough evaluation to determine the source of bleeding. This can be done as an outpatient or the patient can be admitted to hospital, this decision usually dependent upon the hemoglobin level. It is appropriate in this patient to do barium gastrointestinal x-ray studies to determine the possible site of lesion before endoscopy. But endoscopy should follow a noncontributory radiological examination.

The next category is the *acute nonmassive bleeder*. This is the patient who has an acute blood loss from the upper gastrointestinal tract but has not bled enough to cause volume depletion. There is a normal hematocrit and hemoglobin values, coffee ground appearing nasogastric aspirate is present which quickly clears with saline or water lavage. No orthostatic blood pressure nor pulse changes are noted. Stools may be guaiac positive or negative. This patient should be admitted to the hospital for observation and specific therapy. Use of endoscopy within 24 hours will be discussed in a later section, as well as appropriate therapy.

The *acute massive bleeder* represents a medical emergency. In these patients there are normal or decreased hematocrit and hemoglobin levels. The nasogastric aspirate contains bright red blood which does not fully clear with repeated lavage. Orthostatic blood pressure and pulse changes are present and guaiac positive or negative stools may be present in the rectum. The mortality in the acute massive bleeder is significant. In one study[5] a high-risk group of patients were defined: that is, patients over 60 years of age with a presenting hemoglobin value below 10 grams per 100 ml who required greater than 6 units of blood transfusion had a mortality between 20 and 50 percent. A systolic blood pressure below 80 mm of mercury on admission is also associated with increased mortality. The acute massive bleeder should be admitted to an intensive care unit. A central venous pressure line should be placed and blood and volume replacement should be begun. With the patient stabilized endoscopy should be carried out as soon as possible. This will be discussed in a later section. Surgical consultation is imperative in all cases of acute massive bleeding.

Obtaining a Specific Diagnosis

After the initial management a specific diagnosis should be obtained. Barium x-ray studies

TABLE 2.—*Comparison of Urgent Endoscopy and Radiology**

	Endoscopy (Percent)	*Radiology (Percent)*
Allen et al (1973) 71 patients		
positive diagnosis	90	54
correct diagnosis	88	32
Wilken (1973) 69 patients		
positive diagnosis	80	46
correct diagnosis	78	41

*From Truelove and Goodman: Topics in Gastroenterology, 1975[1]

TABLE 3.—*Results of Urgent Endoscopy and Radiology**

	Endoscopy Group	*Radiology Group*
Number of patients	53	105
Diagnosis achieved	96%	37% firm +21% possible
correct	92%	30%
Overall mortality	5.9%	15.2%
Preoperative delay (mean)	2 days	5 days
Operative mortality	14.3%	25.9%
Mean hospital stay in patients not operated upon	11 days	19 days

*From Hoare A: Br Med J 1:27-30, 1975[8]

have no place at present in the early diagnosis of acute upper gastrointestinal blood loss. Forty percent of duodenal ulcers and 50 percent of gastric ulcers will be missed by an upper gastrointestinal series.[6] All acute superficial mucosal lesions will be missed. If more than one lesion is shown present on a barium x-ray study there is no way to definitely know which lesion is responsible for the bleeding. A barium upper gastrointestinal x-ray study may interfere with carrying out arteriography if it is needed in the diagnosis of a massive gastrointestinal hemorrhage. In comparing x-ray studies with endoscopy, recent studies have shown statistically that endoscopy is superior to radiology in obtaining a positive diagnosis (Table 2).[1,7] One recent study has shown that improved overall mortality and improved operative mortality accompany patients in whom diagnosis is made by emergency endoscopy as opposed to those who are handled with a conventional approach (Table 3).[8]

The approach to diagnosis of upper gastrointestinal hemorrhage has changed greatly since the widespread use of flexible fiberoptic endoscopes. The complication rate is low, being estimated at 1.3 per 1,000 cases.[9] Complications are possible and include perforation of the esophagus or stomach, laryngospasm, cardiac arrhythmias in a predisposed patient, aspiration pneumonia and aggravation of bleeding. Upper endoscopy should not be done when a patient is in shock, or when a patient has suffered an acute myocardial infarction or has severe myocardial ischemia as evident on electrocardiogram. Endoscopy should not be done on uncooperative patients or patients with acute respiratory failure. A thoracic aneurysm is a relative contraindication since deaths have been caused by rupture of the aneurysm into the esophagus during endoscopy.[10]

The exact timing of endoscopy in a patient with gastrointestinal blood loss is important for the patient's safety, for making an accurate diagnosis and, practically, in relation to the availability of a physician trained in endoscopy. If endoscopy is done prematurely the patient may still be in shock and may be agitated, both precluding adequate sedation and thereby hampering a satisfactory examination. Adequate gastric lavage is important to prevent retained blood obscuring the endoscopist's view. If endoscopy is delayed for undue lengths of time then the lesion responsible for the bleeding may heal. If more than one lesion is present on delayed endoscopy, all nonbleeding, then occasionally it is impossible to know which was the responsible lesion. Also if endoscopy is delayed, therapy cannot be directed at a specific lesion—this requires the use of endoscopic findings. In one study,[6] endoscopy done within 24 hours of admission gave the diagnosis in 78 percent of cases. Within 48 hours, 66 percent of lesions were diagnosed. When endoscopy was not done until after 48 hours after admission a diagnosis of a bleeding lesion was obtained in only 32 percent of the cases. Therefore optimal timing in carrying out endoscopy would appear to be within 24 hours of an acute nonmassive hemorrhage, and in acute massive hemorrhage endoscopy should probably be done as soon as the patient is adequately lavaged and volume status is corrected as much as possible.

Angiography is important to do in selected cases because it can be therapeutic as well as diagnostic. The patient needs to be actively bleeding at the time of angiography at a rate of greater than or equal to 30 ml per hour in order to visualize extravasation of dye into the bowel lumen which is the only diagnostic sign. Angiography can be done on a rapid bleeder when blood obscures the endoscopist's view, although

TABLE 4.—*Causes of Bleeding in 1,400 Patients With Upper Gastrointestinal Hemorrhage**

	No. of Patients	*Percent of Patients*
Duodenal ulcer	388	27.71
Varices	262	18.71
Gastric ulcer	176	12.57
Gastritis	174	12.43
Esophagitis	93	6.64
Esophagogastritis	16	1.14
Mallory-Weiss syndrome	72	5.14
Anastomotic ulcer	42	3.00
24 other diagnoses	79	5.64
Undetermined or incorrect	98	7.00
TOTAL	1,400	99.98

*From Palmer E: JAMA 207:1479, 1969[2]

most radiologists recommend that angiography should be preceded by endoscopy so that an idea of which artery to initially cannulate can be obtained.[11] In cases of gastric hemorrhage due to ulcer, gastritis, stress ulcer or Mallory-Weiss tear, selective catheterization of the left gastric artery gives the best results.[11] Control of gastric bleeding with left gastric artery infusion of vasopressin occurred in 82 percent of patients with a 16 percent incidence of recurrent bleeding.[12] In esophageal variceal bleeding, superior mesenteric artery vasopressin infusion is effective in a high percentage of cases.[13]

The Possible Diagnosis

Standard gastrointestinal textbooks can be consulted for an extensive list of possible sources of upper gastrointestinal bleeding. Of all the possible lesions, there are about seven common causes of acute upper gastrointestinal hemorrhage. These are esophagitis, esophageal varices, Mallory-Weiss tear, gastritis and gastric erosions, gastric ulcers, duodenal ulcer and stomal ulcer. In various studies the exact frequency of each specific lesion will vary. In an extensive study published by Palmer in 1969 duodenal ulcer was the most common diagnosis being present in 28 percent of patients, with esophageal varices accounting for 19 percent of the cases (Table 4).[2] In a different study at a New York general hospital, acute erosive gastritis was the most common lesion being present in 37 percent of the cases, with esophageal varices being present in 13 percent of the cases.[14] It is important to note that in both studies there was a significant percentage of undiagnosed patients.

Specific Therapy

A guide to the relative merits of the various therapeutic measures in the common causes of gastrointestinal bleeding is illustrated in Table 5.

In esophagitis, elevation of the head of the bed, abstinence from ethanol and tobacco, and small frequent meals are all useful adjunctive therapeutic measures. Hourly antacid therapy is perhaps the most important measure. Metoclopramide can be used to increase the pressure of the lower esophageal sphincter and thereby reduce acid reflux, although this medication is not available in this country at present. Cholinergic medications also have been shown to decrease symptoms by increasing the lower esophageal sphincter pressure.[15] With the advent of cimetidine, pharmacologic efforts aimed at acid reduction may also be helpful. Continuous close monitoring of the patient is the most important therapeutic measure for early detection of recurrent hemorrhage. Anticholinergics should not be used in the treatment of esophagitis since they will increase gastroesophageal acid reflux by lowering esophageal sphincter pressure. The use of pitressin has been advocated, and surgical intervention may be required in a small percentage of cases.

Esophageal variceal bleeding is the cause of death in a third of patients with cirrhosis[4] and in one study variceal bleeding carried a 31 percent mortality.[3] Treatment of variceal bleeding includes volume replacement, although one should be cautious in overenthusiastic or excessive replacement of intravascular volume, in that some studies have suggested that this therapeutic measure may increase portal pressure and lead to increased or recurrent variceal bleeding.[16] Hepatic function should be monitored closely and coagulopathy treated appropriately. Close watch for delirium tremens, withdrawal seizures and hepatic encephalopathy should be maintained. The placement of a Sengstaken-Blakemore tube can temporarily stop esophageal variceal bleeding. Some authors have reported good results with the use of this therapeutic measure.[17] Others have noted a high rate of morbidity and mortality from aspiration pneumonia, asphyxiation and esophageal necrosis.[18,19] The use of vasopressin through a catheter placed with radiologic guidance in the superior mesenteric artery is an alternative to the Sengstaken-Blakemore tube. This procedure has been shown to reduce portal pressure by about

50 percent and, in some reported series, to control variceal bleeding in 85 to 90 percent of cases, although overall survival rate is not altered by the procedure.[13] The use of intravenously given pitressin versus mesenteric arterial administration of pitressin is currently undergoing study. Emergency portacaval shunt surgical procedures to decompress portal hypertension are associated with a mortality approaching 70 percent when done on an emergency basis.[4]

A Mallory-Weiss tear is a mucosal and submucosal tear of the esophagus or stomach at or near the gastroesophageal junction. Some 70 to 90 percent of these tears will heal with medical therapy.[20] The therapy is mainly supportive including volume replacement, frequent antacids and antireflux measures as outlined above under treatment of esophagitis. In 73 to 100 percent of these cases a tear is associated with a hiatal hernia.[20] The tear is often seen with a history of combined salicylate and ethanol ingestion, and the tear is often seen associated with other mucosal abnormalities such as gastritis.[20] Occasionally surgical intervention with oversewing of the tear is necessary to control hemorrhage.

Hemorrhagic gastritis is often seen with the ingestion of salicylates or ethanol, or both. This lesion may bleed massively on occasion; however, it is often controlled with intensive antacid therapy, and volume replacement. Anticholinergics and the use of pitressin may be of some value. Surgical therapy in these patients is tolerated poorly. A total gastrectomy carries a high morbidity and mortality. A lesser surgical procedure such as partial gastrectomy and vagotomy may be satisfactory in controlling hemorrhage in cases of gastritis that do require operation.

The treatment of ulcer diseases such as gastric ulcer, duodenal ulcer and stomal ulcer is basically similar. Antacid therapy and volume replacement and monitoring are the initial important measures. Patients should not be allowed to smoke or to drink caffeinated or noncaffeinated coffee because it has been shown that ulcer healing is impaired by caffeine or coffee consumption or cigarette smoking. The use of cimetidine has been shown to reduce acid secretion and aid in healing acute duodenal ulcers, although studies are needed in cases of gastric and stomal ulcers. Surgical operation in duodenal ulcer disease can effectively control bleeding. The major decision is the type of surgery to do. A vagotomy and pyloroplasty is simple and can be quickly carried out; however, there is a substantial recurrence rate. The operation, consisting of vagotomy and partial gastrectomy, carries a lower recurrence rate but is a more extensive operation and may not be warranted in an acutely bleeding unstable patient.

New Aspects of Therapy in Upper Gastrointestinal Hemorrhage

Perhaps one of the most exciting new aspects in the management of upper gastrointestinal hemorrhage is the advent of therapeutic upper gastrointestinal endoscopy. There are two major mechanisms whereby bleeding can be attacked through the endoscope. The first of these is electrosurgery. Coagulating electrodes are available which can be passed through the conventional endoscope. Coagulation of a bleeding lesion can be done and some researchers have reported good results.[21] Problems include the possibility of a through-and-through burn of the gastric wall producing perforation. Also some researchers have noted increased bleeding in certain cases.[22] Electrosurgery is still considered experimental but is very promising as an additional useful tool in the therapy of upper gastrointestinal hemorrhage. Laser photocoagulation is now being developed.[23,24] It also can be done through the conventional endoscope. Problems include the expense and the fact that the laser equipment is bulky and may not be transported easily. The problem with perforation due to too intense a laser beam

TABLE 5.—*Relative Merits of Various Therapeutic Measures in Common Causes of Gastrointestinal Bleeding*

Therapy	*Esophagitis*	*Esophageal Varices*	*Mallory-Weiss*	*Gastritis*	*Gastric Ulcer*	*Duodenal Ulcer*	*Stomal Ulcer*
Volume replacement and monitoring	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +
Antacids	+ + +	+	+ +	+ + +	+ + +	+ + +	+ + +
Anticholinergics	−	−	−	+	±	+	±
Pitressin	+	+ +	+	+	+	+	+
Ingslaken-Blakemore tube	−	+ +	±	−	−	−	−
Portashunt surgery	±	+	+	±	+ +	+ +	+
Portacaval shunt	−	+ +	−	−	−	−	−

is present. The laser photocoagulation is also considered experimental at this time.

Other modalities for endoscopic control of hemorrhage that have been tested but have not been proved yet to be of definitive value are the following: tissue adhesives;[25-28] intragastric instillation of norepinephine, 8 mg in 100 mg of saline;[29] vasopressin or prostaglandin,[30] and compressed air causing a local drying effect.[31] Other modalities that require special skills and training include the use of sclerosing agents,[32] the use of hemoclips, transhepatic embolization of esophageal varices[33] and cryosurgery.[34] These newer techniques should be carefully assessed before becoming part of the armamentarium for the treatment of gastrointestinal bleeding.

Conclusions

In the management and diagnosis of upper gastrointestinal hemorrhage, initial management is important in stabilization of the patient so that diagnostic measures can be safely undertaken. Although the overall mortality in upper gastrointestinal hemorrhage has remained stable at 8 to 10 percent over the last 25 years, newer studies are beginning to show improved survival with the aggressive use of fiberoptic endoscopy. The era of therapeutic endoscopy is on the horizon and will undoubtedly play a major role in the treatment of acute upper gastrointestinal hemorrhage in the future.

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Tendon Ruptures Associated With Corticosteroid Therapy

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In five patients, tendon ruptures occurred in association with corticosteroid therapy, either systemic or local infiltration. The chronic nature of the pain in all of these patients suggests that what we often call tendinitis may in fact be early or partial ruptures of tendons. Patients who receive local infiltration of corticosteroids should perhaps be advised of the risk of a ruptured tendon. In addition, particularly when the Achilles tendon is involved, immobilization should be utilized initially for a presumed tendinitis or early rupture, to protect the tendon from further injury.

RUPTURE OF TENDONS has been previously described in association with corticosteroids, whether given systemically or by local infiltration. In most cases, it is difficult to establish whether the injury is due to the therapy or the primary disease for which the steroids were given. Local infiltration is often given for a supposed tendinitis, which may be the first indication of an early or partial rupture. Five cases are presented which illustrate some aspects of this complex interaction, and the variability with which the clinical picture may present.

Reports of Cases

CASE 1: A 34-year-old decathlon athlete was admitted to Stanford University Medical Center with a rupture of his left patellar tendon sustained during high jumping. Three years before this admission, he had had a knee strain, and was treated with a corticosteroid injection to the infrapatellar area. For the next year, he continued to train and there was no recurrence of his pain. However, the parapatellar pain recurred and the patient was given three additional injections, the most recent three weeks before admission. On surgical operation it was found that the patellar tendon was torn from the inferior pole of the patella. It was repaired and the patient placed in a posterior splint.

CASE 2. A 32-year-old man was seen in the emergency room after he felt a "snap" in his left knee while high jumping. He had swelling and pain in the left knee area and was unable to bear weight on his leg. On physical examination at the time of admission a complete rupture of the left patellar tendon was noted.

Approximately six years before admission the patient was seen at a community hospital for pain in his left knee. Over the next few months five to ten injections of steroid compounds were given into the lateral parapatellar area overlying the tibial condyle; the pain was relieved. The pain subsequently returned two years later, at which time examination disclosed tenderness along the medial border of the patella. A diagnosis of

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Figure 1.—The muscle belly of the long head of the biceps protrudes after tendon rupture in case 3 (photo by Dr. J. Stenger).

chondromalacia was made and the patient was begun on a program of quadriceps exercises. Two years before admission a meniscectomy had been carried out for a tear of the right medial meniscus. The patient had been bothered by pain in that knee since then and had been taking indomethacin.

The patient was taken to surgery, where a complete rupture of the left patellar tendon from its attachment to the tibial tubercle was found. The tear was repaired and the patient was placed in a cylinder cast.

CASE 3. A 51-year-old man was seen in the ambulatory emergency room with a three-year history of chronic pain in both shoulders. There was tenderness over the long head of the biceps tendon of both arms. Three weeks before being seen in the orthopedic clinic, both tendons were injected with a mixture of dexamethasone crystalline suspension and lidocaine, with immediate relief of the pain. Two weeks later, the patient made a sudden turn while driving his truck, producing increased pain in the area of the right biceps tendon. Five days following this he noted weakness of flexion of the right arm and a lump in the area of the biceps muscle. He subsequently was seen in our clinic with a complete rupture of the long head of the biceps and a mass distal to the rupture (Figure 1). The patient was treated conservatively with a program of graded exercises.

It was noted in the patient's medical history that a diagnosis of ulcerative colitis had been made in 1966, for which cortisone was given for a period of six months.

CASE 4. In a 26-year-old woman with systemic lupus erythematosus, pain and swelling developed in the right knee after she fell off a haystack. The patient was not able to bear weight on the knee, but was able to flex and extend it. She described feeling that the patella was dislocated momentarily and that she put it back in place. The patient was seen in the emergency room with a swollen ecchymotic knee with an active range of motion of 15 to 45 degrees. The cruciate and collateral ligaments were intact. There was tenderness at the insertion of the patellar tendon, but there was no gap in the continuity of the quadriceps mechanism. Roentgenographic examination disclosed no bony abnormalities. The patient was given a knee immobilizer and seen two weeks following the injury, at which time she began walking, with full weight-bearing.

Six weeks following the injury the patient was seen again, with complaint of persistent knee pain. She lacked 30 degrees of active extension, but had full passive extension. She was begun on a program of exercises and continued to show improvement, walking with only minimal difficulty.

Approximately three months following the initial injury, she experienced sudden pain in the knee, and was unable to bear weight or to fully extend the knee. When the patient was seen in the orthopedic clinic there was a pronounced indentation of the quadriceps mechanism at the level of the tibial tuberosity. Rupture of the patellar tendon was diagnosed and the patient was admitted to the hospital.

The patient's lupus symptoms date to approximately age 10. For the past year she had been taking prednisone in doses ranging from 5 to 15 mg per day. In addition, she took hydrochlorothiazide and hydroxychloroquine sulfate. At age 12, an arrhenoblastoma was removed and the patient recovered uneventfully with full endocrine function.

The patient was taken to surgery where a partial avulsion of the patellar tendon from the tibial tuberosity was found. Approximately 85 percent of the tendon was avulsed from its insertion. Two smooth Steinmann pins were then placed through the patella and proximal tibia to secure the repair (Figure 2).

CASE 5. A 34-year-old man was admitted to the orthopedic service of the Stanford University Medical Center for a rupture of the right Achilles tendon.

Approximately four years before admission,

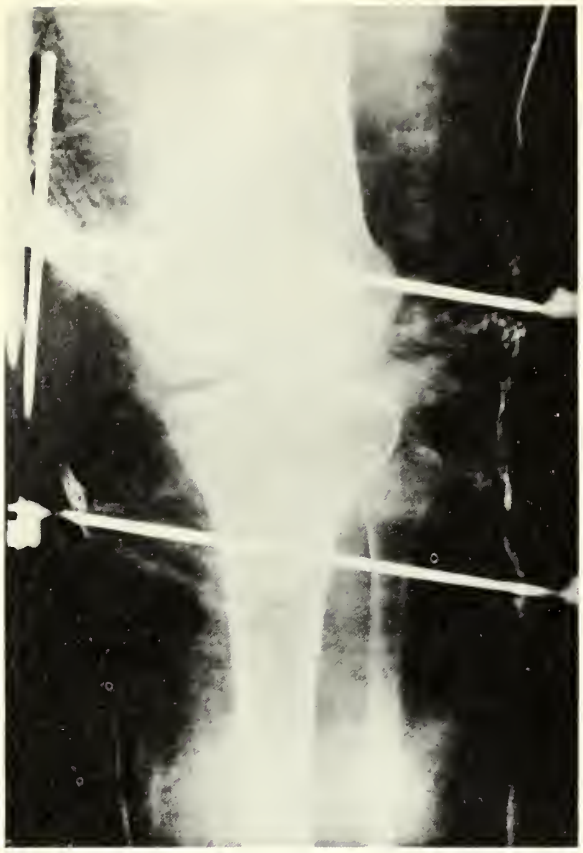

Figure 2.—Steinmann pins are placed through the patella and the proximal tibia to insure immobilization during the repair of the patellar tendon in case 4.

pain developed in the area of the Achilles tendon after the patient jumped off a fence. The pain persisted and was exacerbated by running or standing in hard shoes. Roentgenograms taken in the orthopedic clinic showed a spur on the calcaneus. There was also tenderness over the insertion of the Achilles tendon. A diagnosis of tendinitis was made and an injection of 2 ml of 1 percent lidocaine with 1 ml of methylprednisolone acetate was made into the tender area. The patient noted some relief and three weeks later the injection was repeated. The pain improved and the patient was essentially pain free for five months. He was then seen in the orthopedic clinic in 1974, again with complaint of pain in the area of the Achilles tendon. The patient's ankle was taped, but this provided little relief. The tendon was then injected with 3 ml of 1 percent lidocaine and 2 ml of methylprednisolone acetate at the site of the pain. In June of 1975 the pain was exacerbated by jogging. At this time a small lump was noted over the area of the right Achilles tendon at the point of maximum discomfort. The patient was subsequently seen four months after that examination with recurrence. Ice and high dose acetylsalicylic acid therapy provided little relief. A short-leg walking cast was applied for three weeks, with pronounced relief during the period of immobilization. However, the week following removal of the cast, the pain recurred and the patient was treated with phenylbutazone for one week. There was no improvement, and treatment was carried out with injection of 3 ml of 1 percent lidocaine and 1 ml of hydrocortisone. All symptoms subsided three weeks following the injection.

In May of 1976 the symptoms recurred and the patient was again seen in the orthopedic clinic. Physical examination disclosed point tenderness at the insertion of the Achilles tendon. The area of maximal tenderness was injected with lidocaine and methylprednisolone. In June of 1976, after a day of strenuous exercises, the patient ruptured his Achilles tendon while walking. On surgical operation, a complete rupture of the Achilles tendon was seen approximately 1½ cm above its insertion. The tendon was repaired primarily, and the patient was placed in a plantar flexed short-leg cast.

Discussion

A growing number of cases of tendon ruptures associated with corticosteroid therapy has been reported (Table 1). In most of the cases the indication for therapy has been a collagen vascular disease. While tendon ruptures are found in patients with rheumatoid arthritis, often associated with corticosteroid therapy, Tarr—in presenting four cases—notes that bony spurs, granulomatous invasion of rheumatoid tissue along the tendon, and necrosis of the tendon secondary to ischemia from either hypertrophic tissue or vasculitis may also contribute to ruptured tendons.[1]

The cases of Smaill[2] and Melmed[3] are particularly noteworthy in that the patients were given corticosteroids for respiratory difficulties, not a disease associated with compromise of the tendon itself.

Local corticosteroid infiltration has also been implicated as a contributing factor, if not a cause, of tendon ruptures. Ismail and associates reported a case of a 25-year-old high jumper in whom pain developed over the left patellar tendon.[4] A provisional diagnosis of tendinitis was made and the patient was treated with shortwave diathermy and multiple infiltrations of the ligament with corticosteroids and lidocaine. The pain was re-

lieved temporarily but the patient continued his high jumping. More than a year after the initial presentation with pain, the patient, while high jumping in a training session, slipped and felt his left knee give way. The patellar tendon was found at surgical operation to be ruptured through its substance about 2½ cm above the insertion.

Bedi and Ellis described a 48-year-old woman with rheumatoid arthritis in whom a spontaneous rupture of the left Achilles tendon occurred after local administration of corticosteroids for an acute flare-up of rheumatoid arthritis.[5] The patient had received one injection of methylprednisolone acetate into both tendocalcaneal insertions, with a second injection into the left heel three weeks after the initial symptoms. There was notable relief of pain after the injections. At operation, a complete avulsion of the tendon from the calcaneal attachment was found.

A number of studies have shown that tendons which eventually rupture may present varied and prolonged clinical features.[6,7] Fox and co-workers, in discussing ruptured Achilles tendons, noted 22 patients whose complaints extended for as long as two years.[8] No note was made as to the treatment they had received during this time.

The exact mechanism by which corticosteroids might predispose to tendon rupture is not certain. However, there is some experimental evidence indicating that corticosteroids do inhibit the healing process of tendons. Wrenn and associates, in an experimental study of the effect of cortisone on the healing process and tensile strength of tendons, found that corticosteroid therapy, though not completely inhibiting the healing process, did decrease some of the fibrous tissue and reduced the strength of the repaired tendon by 40 percent.[9] In addition, the regeneration of the tendon sheath was delayed during the administration of cortisone.

Most doubt that a normal tendon would rupture as a result of the stress caused by the injuries that many of the patients describe. In the collagen vascular diseases, such as systemic lupus erythematosus or rheumatoid arthritis, it is not at all clear whether this predisposition results from the primary disease or from the corticosteroid therapy. Lotem and co-workers believe that some distinction can be made by histologic examination of the rupture site to determine whether there was an inflammatory process present.[10]

Salter and Murray found that when hydrocortisone was injected into the calcaneal tendon of rabbits it was absorbed slowly and provided evidence of fatty degeneration.[11] Balusubramaniam and Prathap also looked at the effect of injecting hydrocortisone into rabbit calcaneal tendons.[12] They found that in the acute inflammatory phase, 24 to 72 hours following injection of hydrocortisone into the tendon, the injected tendon showed areas of collagen necrosis. Lesions closer to the paratendon showed vasodilation and acute polymorphonuclear cell response, while lesions centrally placed on the tendon showed very little, if any, cellular response. Their study showed the direct effect of hydrocortisone in producing collagen necrosis at the site of injection.

The cases presented in this report illustrate many of the varied clinical features seen with ruptured tendons.[13] The patient with the ruptured biceps tendon, a truck driver who frequently needed to abduct and externally rotate his arm

TABLE 1.—*Previously Reported Cases of Tendon Ruptures Associated with Corticosteroid Therapy*

Author	*Primary Disease*	*Medication*	*Injury*
Morgan and McCarty[15]	SLE	40 mg, prednisone	Patellar tendon extensor digitorum communis
Woodward and Sliwinski[16]	SLE	15 mg, prednisone	Achilles tendon
Wener and Schein[17]	SLE	30 mg, prednisone	Bilateral patellar tendon
Twining et al[18]	SLE	60 mg, prednisone	Quadriceps & patellar
Martin et al[19]	SLE	125 mg, prednisone	Bilateral patellar tendon
Lotem et al[9]	SLE	30 mg, prednisone	Extensor tendon fourth digit
Lee[20]	SLE	prednisone	Bilateral Achilles tendon
Rascher et al[21]	SLE	15 mg, prednisone	Bilateral patellar tendon
Razzano et al[22]	RA	7.5 mg, prednisone	Bilateral patellar tendon
Smaill[2]	Asthma	10 mg, prednisone	Bilateral Achilles tendon
Cowan and Alexander[23]	Discoid lupus	16 mg, triamcinolone	Bilateral Achilles tendon
Melmed[3]	Respiratory distress	betamethazone	Bilateral Achilles tendon
Ismail[4]	Tendinitis	local triamcinolone	Patellar tendon
Bedi and Ellis[5]	RA	local prednisolone	Achilles tendon

SLE = systemic lupus erythematosus
RA = rheumatoid arthritis

(an exercise particularly stressful to the long head of the biceps), had complaint of pain in that area for three years. Only following the injection of corticosteroids, with moderate relief of pain and presumably increased use of the extremity, did a rupture occur. This patient is particularly fearful of a rupture on the opposite side, as the symptoms are identical.

The cases of the patients with patellar ligament ruptures are quite similar to a case described by Ismail and co-workers: All patients had received multiple injections of corticosteroids into the substance of the patellar tendon and sustained a rupture while high jumping.[4] In these cases the pain relief provided by the corticosteroid and the lidocaine may have allowed the patients to resume normal activities which they might not have, given normal physiological processes.

In the patient with the ruptured Achilles tendon, it is likely that what was diagnosed as tendinitis may very well have been a series of microruptures in the tendon, causing chronic pain. The pronounced improvement that occurred while the patient was in the cast supports this view. The chronic pain in the Achilles tendon, coupled with our inability to distinguish true tendinitis from what may be an early partial rupture, seems to indicate that the treatment for both a partial rupture and tendinitis should be immobilization. It would also appear, at least from the reports of other authors in treating ruptures of Achilles tendons by closed methods, that only immobilization for a period of six to eight weeks will result in successful therapy of this problem.[14]

In the patient with systemic lupus erythematosus, who was receiving oral prednisone, it is interesting to note that there was a reasonable amount of function with only a portion of the tendon intact. It appears that a significant portion of the tendon was ruptured only months after the original injury. It is not known whether the continued corticosteroid therapy interfered with the normal repair of the tendon while in the cylinder cast, as might have happened in a person not receiving this medication.

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Hemoptysis: Diagnosis and Management

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Hemoptysis is one of the most important symptoms of cardiopulmonary disease—first, because bleeding even in small amounts may indicate the presence of such serious diseases as bronchogenic carcinoma or active tuberculosis, and second, because untreated massive hemorrhage is associated with a high mortality rate. The cause of hemoptysis may be suggested by the history, physical examination or chest x-ray findings, but often diagnostic procedures such as bronchoscopy, bronchography and pulmonary angiography are needed for definitive diagnosis. The importance of early localization of the bleeding site and surgical intervention in patients with massive hemoptysis is stressed.

HEMOPTYSIS IS A common symptom of cardiopulmonary disease, being reported by 7 to 15 percent of patients evaluated in chest clinics.[1-14] Although bronchitis is a very common cause of hemoptysis, a thorough evaluation is usually necessary to exclude the presence of more serious pathologic conditions such as tuberculosis or bronchogenic carcinoma. The amount of bleeding that a patient reports, even merely blood-streaked sputum, does not influence the need for full investigation since the quantity of blood may not be correlated with the seriousness of the underlying thoracic disease.[1-3,5]

Hemoptysis was concisely referred to in the Hippocratic aphorism "the spitting of pus follows the spitting of blood, consumption follows the spitting of this and death follows consumption."[2] For centuries, hemoptysis was considered pathognomonic of pulmonary tuberculosis. In 1936 Würtzen and Sjorslev noted, however, that a third of patients admitted to a tuberculosis sanitarium for hemoptysis did not have tuberculosis as previously assumed.[6] It has recently become quite clear that there are actually numerous causes of hemoptysis. The more common or well-known (or both) of these are given in Table 1. A more complete list was published by the American Thoracic Society in 1966.[7]

There are no recently collected epidemiologic data on the relative frequency of the various causes of hemoptysis. American studies, reported two to three decades ago, indicated that bronchitis or bronchiectasis (or both), lung carcinoma, and tuberculosis were the most common causes of hemoptysis (in that order), and accounted for over two thirds of the cases.[2,8] Lung carcinoma no doubt continues to be a major cause of hemoptysis in the United States, since a recent American Cancer Society study reports a 14-fold increase in lung cancer in the last 40 years.[9] A parallel increase in cigarette smoking implies the same is true of bronchitis.[9] In contrast, the incidence of tuberculosis has decreased in the United States, although in some other parts of the world it

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TABLE 1.—*Common or Well-Known Causes of Hemoptysis*

Arteriovenous aneurysm	Parasitic infection
Bleeding diathesis	Pneumoconiosis
Bronchial adenoma	Pneumonia (viral, bacterial, fungal)
Bronchial endometriosis	Polyarteritis nodosa
Bronchitis	Primary pulmonary hypertension
Bronchiectasis	Pulmonary edema due to left ventricular failure or mitral stenosis
Bronchoaortic artery fistula	Pulmonary infarction
Bronchogenic carcinoma	Systemic lupus erythematosus
Broncholithiasis	Trauma
Bronchopleural fistula	Tracheal-innominate artery fistula
Chronic granuloma of lung	Transthoracic and transbronchial lung biopsy
Congenital heart disease	Transtracheal aspiration
Cystic fibrosis	Tuberculosis
Cysts and blebs	Wegener granulomatosis
Foreign body	
Goodpasture syndrome	
Idiopathic pulmonary hemosiderosis	
Lung abscess	
Metastatic carcinoma	
Mycetoma	

remains poorly controlled and is still the main cause of hemoptysis.[3]

The percentages of patients with specific intrathoracic diseases having hemoptysis are shown in Table 2. Hemoptysis is most closely associated with aspergilloma, bronchiectasis, bronchial adenoma and bronchogenic carcinoma.

Pathophysiology of Hemoptysis

There are numerous pathophysiologic mechanisms that result in bleeding from the tracheobronchial tree. For example, inflammation of the mucosa (vascular engorgement, desquamation, atrophy and erosion) as in acute or chronic tracheobronchitis commonly results in bleeding. The mucosa of the tracheobronchial tree is well vascularized and quite friable. Mild trauma such as produced by suctioning during bronchoscopy is often sufficient to result in active bleeding.

Infarction of lung tissue often results in hemoptysis. Pulmonary infarction may be due to bland and septic pulmonary emboli; invasion of blood vessels by Pseudomonas aeruginosa, phycomycosis and Aspergillus fumigatus; pulmonary vasculitis such as polyarteritis nodosa, Wegener granulomatosis and systemic lupus erythematosus; and necrotizing staphylococcal, Gram-negative or fungal pneumonia.

In acute left ventricular failure or mitral stenosis, blood-streaked sputum is due to rupture of pulmonary veins or capillaries distended by elevated intravascular pressure. In addition, enlarged bronchial veins may be the source of bleeding in mitral stenosis.[15]

TABLE 2.—*Percentage of Patients With Specific Intrathoracic Diseases Having Hemoptysis**

Diseases	*Percent of Patients With Hemoptysis*
Aspergilloma	55-85
Bronchial adenoma	46-55
Bronchogenic carcinoma	37-53
Bronchiectasis	28-45
Lung abscess	11-15
Tuberculosis	6-19

*See References 3, 10-14, 23, 26, 27, 48.

Hemorrhage in Goodpasture syndrome is due to abnormalities in the alveolocapillary basement membrane, possibly due to antibody directed to the membrane.

Hemoptysis is associated with active tuberculosis. However, it may occur years after the disease has been adequately treated from any of the bronchopulmonary sequelae of previous tuberculous infection, including broncholithiasis (rupture of a calcified lymph node into a bronchus), development of a carcinoma (adenocarcinoma) in a tuberculous scar, bronchiectasis, and a residual cavity with or without a mycetoma.[16]

Bleeding from a tuberculous cavity, whether the infection is active or arrested, has been attributed to rupture of a Rasmussen aneurysm, a pear-shaped dilatation of a pulmonary or bronchial artery in the wall of the cavity.[17] However, Thompson studied 138 patients with tuberculosis dying of pulmonary hemorrhage and found only eight instances of aneurysmal dilatation of arteries lining the blood-filled tuberculous cavity.[18] Rather than being due to distinct aneurysmal dilatation of a bronchial or pulmonary artery, hemoptysis in patients with cavitary tuberculosis is more likely related to the development of a hypervascularized, dilated, tortuous bronchial circulation, and to anastamoses between the bronchial and pulmonary circulations. These vascular abnormalities have been well shown in autopsy specimens and by antemortem selective bronchial arteriography in patients with cavitary tuberculosis as well as in patients with other chronic pathological conditions including bronchiectasis, cystic fibrosis and lung abscess.[19-22] Hemoptysis, often massive, in these patients has been postulated to occur as a result of rupture of pulmonary capillaries (possibly due to entrance of high pressure bronchial blood into the low pressure pulmonary

TABLE 3.—*History in Patients With Hemoptysis*

Age of patient
Time of onset of hemoptysis in relation to duration of other symptoms
Chest pain
History of cardiopulmonary disease
History of cigarette smoking
History of hematuria
Appearance of sputum
Symptoms of nasal, oropharyngeal, laryngeal disease, or gastrointestinal disease

circulation) or dilated bronchial arteries that are adjacent to areas of chronic inflammation and infection.[21,22]

In cases of bronchogenic carcinoma, pathologic studies have shown an increase in the bronchial arterial supply to the region of the tumor.[20] Selective bronchial arteriography, however, has shown there to be abnormalities in the bronchial circulation in only five of 158 patients with lung carcinoma.[21] It is unlikely that hemoptysis in patients with bronchogenic carcinoma is due to rupture of large bronchial arteries or bronchopulmonary anastamosis since hemorrhage in these patients is usually mild, and rarely massive. Malignant tumors of the lung more likely produce hemoptysis by invasion of the mucosa or by necrosis of tumor tissue.

The pathogenesis of bleeding from a mycetoma (proliferation of a fungus such as aspergillus, nocardia or candida in an air-filled cavity) is not known. A number of pathogenic mechanisms have been suggested, including friction caused by movement of the mycetoma, and release of an anticoagulant and trypsin-like proteolytic enzyme from the fungus.[23]

Hemoptysis associated with closed chest trauma is usually due to contusion of the lung parenchyma; that is, exudation of blood and edema fluid into the intraalveolar spaces as well as interstitium.[24] Less frequently, bleeding following closed chest trauma, particularly to the anterior chest, results from fracture of the trachea just above the carina or of one of the mainstem bronchi just below the carina. Finally, hemoptysis following a penetrating bullet wound to the chest occurs when there is a communication between the missile track and the bronchial tree.

Clinical Evaluation of Hemoptysis

The evaluation and treatment of patients with hemoptysis depends on many factors, the most important of which is the rate of bleeding. There is generally ample time for evaluation of cause and management when bleeding is not massive. When hemorrhage is massive (200 to 600 ml of blood in 24 hours), localizing the site of bleeding and specific therapy (including maintenance of an airway, transfusion and surgical operation) should progress simultaneously with diagnostic studies to determine the cause of the bleeding or occasionally should precede them when necessary.

History

A thorough history may provide clues to the site of bleeding and the underlying disease. Table 3 lists some of the important points in the history.

The age of the patient at the onset of hemoptysis is helpful since some causes are age-related. Andosca and Foley pointed out that bronchiectasis and mitral stenosis were significant causes of pulmonary hemorrhage before age 40,[25] whereas bronchogenic carcinoma is more commonly the cause after age 40.[8]

The time of onset of hemoptysis in relation to the duration of other pulmonary symptoms may be of some diagnostic value. For example, hemoptysis is rarely the initial symptom in bronchogenic carcinoma[5,26,27] and, as a matter of fact, usually occurs late in the sequence of symptoms, being preceded by a change in cough pattern, fatigue and vague chest sensations.[27] Hemoptysis occurs earlier when a tumor arises in a major bronchus than when it is more peripheral.[8]

A patient may occasionally describe subjective chest sensations at the time of hemoptysis, including burning, heaviness, bubbling and vague chest pain. These sensations may localize the site of bleeding to one lung or even to a specific lobe.[5,27,28]

A history of hematuria in a patient presenting with hemoptysis suggests the presence of such diseases as Wegener granulomatosis, Goodpasture syndrome and polyarteritis nodosa.

The appearance of sputum may occasionally be of some value. Blood mixed in with gritty white material suggests the diagnosis of broncholithiasis. Frothy pink sputum is seen in pulmonary edema due to left ventricular failure. Rusty brown or prune juice colored sputum is seen in bacterial pneumonia. Blood mixed with pus is more likely to be due to lung abscess or pneumonia if the illness is acute or semiacute, whereas bronchiectasis is more likely if the illness is chronic. Blood streaking of mucoid sputum is not of diagnostic help, since it may be due to a variety

TABLE 4.—*Important Physical Findings in Patients With Hemoptysis*

Clubbing
Telangiectasia
Petechiae, ecchymosis
Ulceration of nasal septum
Diastolic rumble, opening snap
Adenopathy
Localized wheezes, rhonchi, rales

of disorders including bronchitis, tuberculosis and bronchogenic carcinoma. Two conditions may be associated with sputum that contains no blood but may be confused with hemoptysis. Patients with pneumonia due to Serratia marcescens, a Gram-negative rod which is occasionally pigmented red, may produce red sputum which does not contain red blood cells and which is hematest negative. An amoebic abscess may rupture into a bronchus and cause the expectoration of "anchovy paste" sputum, resembling old blood.

It should be emphasized that bleeding may be from the nasal passages, nasopharynx, gums or larynx, rather than the lung. Laryngoscopy may be required to differentiate upper from lower respiratory tract bleeding. Hematemesis is occasionally reported as hemoptysis by patients. Suctioning blood or guaiaic positive material from the stomach via a nasogastric tube may not reliably differentiate gastrointestinal from tracheobronchial bleeding, since patients with hemoptysis frequently swallow coughed blood.

Physical Examination

Physical examination should include a specific search for the findings listed in Table 4. Telangiectasia on the lips or buccal mucosa is seen in Rendu-Osler-Weber disease. Clubbing is associated with bronchogenic carcinoma, bronchiectasis and lung abscess, as well as many other pulmonary and nonpulmonary disorders. A diastolic rumble and opening snap indicate the presence of mitral stenosis. Palpable cervical, scalene or supraclavicular lymph nodes suggest bronchogenic carcinoma. Ulceration of the nasal septum and other midline structures of the upper airway are seen in Wegener granulomatosis. Localized rales, wheezes, and ronchi should be interpreted with caution since these physical findings may represent pneumonitis due to aspirated blood rather than indicate the site of active bleeding.

Laboratory Studies

Table 5 lists laboratory studies that are most helpful in evaluating patients presenting with

TABLE 5.—*Essential Laboratory Studies in Patients With Hemoptysis*

Complete blood count, differential, platelet count
Prothrombin time, partial thromboplastin time
Urinalysis
Sputum smear and culture for bacteria, acid fast bacteria, and fungus
Sputum cytology
Intermediate-PPD (coccidioidomycosis and histoplasmosis skin tests, serologies in endemic areas)
Aterial blood gases (in selected patients)
X-ray film of chest

hemoptysis of unknown cause. Roentgenographic examination of the thorax should be obtained routinely in all cases of hemoptysis. Frequently, the pathologic process responsible for hemoptysis will have a typical roentgenographic appearance which is not obscured by aspirated blood. Examples are the enlarged left atria and Kerley B lines of mitral stenosis, an old tuberculous cavity containing a movable mass suggestive of an aspergilloma, or a central mass associated with loss of lung volume distal to the mass suggestive of a bronchogenic carcinoma. Great caution should be exercised in ascribing the site of bleeding to an abnormality, shown on x-ray study of the chest, that could be associated with hemoptysis. At bronchoscopy, the bleeding site has occasionally been identified elsewhere.[28]

The finding of no abnormalities on an x-ray film of the chest in a patient with hemoptysis should not preclude the consideration of additional diagnostic studies such as bronchoscopy and bronchography. Hemoptysis may occasionally be the only clinical indication of the presence of a bronchogenic carcinoma[30,31] or bronchiectasis.[30]

All expectorated sputum should be collected in a container placed at the patient's bedside. This will allow both qualitative examination of the sputum (such as for presence of pus) and measurement of the quantity of expectorated blood. The latter is particularly important since the patient's estimation of the amount of hemoptysis is often erroneous.

Special Procedures

Bronchoscopy

Hemoptysis is reported to be the most common indication for endoscopic examination of the tracheobronchial tree.[33] Although other studies are helpful in establishing the site and cause of the hemoptysis, bronchoscopy is often needed for both definitive diagnosis and localization. In patients with mild to moderate bleeding, bronchos-

copy has in our experience been used primarily to exclude bronchogenic carcinoma as the cause. In many cases of nonmassive hemoptysis, the cause is obvious and bronchoscopy is not necesary. Examples include active tuberculosis, pneumonia, pulmonary infarction, bronchiectasis and acute tracheobronchitis. However, even in these pulmonary disorders, if the bleeding is persistent or recurrent, a bronchoscopic evaluation may be required to exclude the presence of a tumor.

Bronchoscopy should be done in all patients with massive hemoptysis to identify the bronchial orifice from which active bleeding is coming; determination of the cause is often less important in the emergency management of the patient. Direct bronchoscopic visualization of the site of bleeding in patients with life-threatening hemoptysis cannot be replaced by the history, physical examination or x-ray film of the chest, which can only suggest the bleeding site,[29] or even by knowledge of a previously known cause and site of bleeding. If an emergency operation becomes necessary to control bleeding, knowledge of the exact site of bleeding is obviously essential.

Whether bronchoscopy should be done during the period of active bleeding has been controversial. Jackson and Diamond recommended that bronchoscopy be postponed until after hemoptysis has subsided for fear of reactivating bleeding.[26] However, the consensus is that bronchoscopy is both safe and highly informative during the period of active bleeding.[2,29,34] Pursel and Lindskog were able to visualize the site of bleeding with a rigid bronchoscope in 86 percent of a group of patients bleeding actively at the time of the procedure, while the bleeding site was identified in only 52 percent of patients in whom active hemoptysis was not present.[2] Using fiberoptic bronchoscopy during the period of active bleeding, Smiddy and co-workers located the source of bleeding in 66 of 71 patients;[29] Rath identified the site of bleeding in 21 of 31 patients.[34] Bronchoscopy did not produce deleterious effects in any of the patients in these three series. These data suggest that there is an advantage to bronchoscopy during active bleeding and that there is relatively little risk.

The fiberoptic bronchoscope has replaced the rigid bronchoscope for evaluation in patients with nonmassive hemoptysis since it is flexible and allows visualization of segmental and subsegmental bronchi, thus increasing the diagnostic yield. In patients with massive hemoptysis, Smiddy and associates successfully visualized the site of active bleeding by systematically lavaging segmental bronchi with a fiberoptic bronchoscope.[29] Despite this recent report, many bronchoscopists still favor the use of the rigid metal bronchoscope during massive hemoptysis,[33,35] since it is easier to maintain vision through the rigid bronchoscope because it has a large channel for aspirating blood. In addition to its diagnostic value, the rigid metal bronchoscope can be used to suction blood clots from the tracheobronchial tree, maintain an airway, provide mechanical ventilation and control hemorrhage (see section on massive hemoptysis, later in the article).

Tomography

Tomography may be of value in selected cases to better show the presence of lung cavities, solid masses, and mediastinal and hilar adenopathy. If broncholithiasis is suspected, tomography may be helpful in demonstrating the antomical relationship of a calcified lymph node to the bronchi.[5]

Ventilation-Perfusion Lung Scanning/Pulmonary Angiography

In patients presenting with the sudden onset of hemoptysis, dyspnea, and pleuritic chest pain, lung scanning or pulmonary angiography, or both, may be needed to diagnose pulmonary infarction. In addition pulmonary arteriovenous anastamoses, which may be responsible for hemoptysis in patients with or without Rendu-Osler-Weber disease, may be visualized by pulmonary angiography. The presence of a pulmonary arteriovenous communication is suggested roentgenographically by the appearance of a somewhat lobulated sharply defined round or oval homogeneous density which decreases in size during the Valsalva maneuver.

Bronchography

In patients with unexplained recurrent hemoptysis, a chronic cough productive of purulent sputum, and abnormalities shown on an x-ray film of the chest, bronchography should be considered to determine the presence and extent of bronchiectasis. A normal finding on an x-ray study or absence of a productive cough does not exclude bronchiectasis as a possible cause of hemoptysis. In one study 7 percent of patients with significant bronchiectasis had normal roentgenograms,[36] while in another study, 22 patients or 3 percent of all patients with bronchiectasis had no history

of a chronic productive cough or recurrent acute respiratory tract infection; that is, had so-called "dry bronchiectasis."[32] It is significant that in this group of patients with "dry bronchiectasis," hemoptysis was present in approximately half.

Bronchography should generally be done after active bleeding has subsided. During active bleeding or after recent bleeding, the procedure not only is technically difficult but results may be misleading, since clots within the bronchi may cause irregularities of contour or a failure of normal filling.[2,5,8] Furthermore, the injection of a bronchographic dye may produce additional respiratory embarrassment in a patient who is actively hemoptysizing and aspirating blood.[37,38]

Selective Bronchial Arteriography

Selective bronchial arteriography (SBA) was recently used in an attempt to identify the site of massive pulmonary hemorrhage in six patients with cystic fibrosis.[22] Extravasation of contrast medium was observed in one patient and in two others enlarged bronchial arteries were found in a single lobe. Findings on selective bronchial arteriography correlated well with bronchoscopic localization of the bleeding site. In the remaining three patients, SBA was normal or showed diffuse abnormalities of the bronchial vasculature.

Selective bronchial arteriography may be of value if bronchoscopy has failed to identify the site of massive bleeding. However, since experience with SBA is limited, it should not supplant bronchoscopy which remains the most reliable method of localizing pulmonary hemorrhage.

Hemoptysis of Unexplained Cause

The relative frequency of unexplained hemoptysis in various studies has ranged from 0.5 to 58 percent with most values in the range of 5 to 15 percent.[1,2,4,8,26] This variability is due to a number of factors, the most important of which are methods of patient selection and the diagnostic methods employed.

The clinical course of patients presenting with an episode of unexplained hemoptysis was investigated by Douglass and Carr.[39] Fifty-five patients who had hemoptysis for which no cause was found on x-ray films of the chest, bronchoscopy and bronchography were followed for five more years. Nineteen of the patients had additional episodes of bleeding, all but one less in quantity than during the initial episode. However, only one patient was subsequently found to have bronchogenic carcinoma, indicating that patients with unexplained hemoptysis after thorough evaluation have an excellent prognosis for having a benign lesion. These findings were confirmed by Barrett and associates who followed 81 patients with hemoptysis of unknown cause.[40] It is probable that most hemoptysis of unknown origin is due to minor inflammatory disease, such as bronchitis, which is present beyond the field of the bronchoscope, or less frequently to mild bronchiectasis not detected by bronchography.[39]

Massive Hemoptysis

Whether or not hemoptysis should be called massive has usually been arbitrarily based on the amount of blood expectorated. Critical amounts have ranged from 200 to greater than 600 ml in 24 hours.[2,5,41-43] This is a critical definition, since the diagnosis of massive hemoptysis has served as a guideline for the necessity for immediate surgical intervention. However, it is important to note that the mortality rate for pulmonary hemorrhage is more closely related to the severity of obstruction of the tracheobronchial tree than to the amount of blood loss.[5,44-46] For example, in an obtunded or debilitated patient or in a patient with underlying chronic pulmonary disease, the quantity of blood hemoptysized may be less than that defined as "massive" and yet still be life-threatening.

Chronic inflammatory pulmonary diseases can cause severe bleeding, especially when associated with destruction of pulmonary tissue. It is, therefore, no surprise that tuberculosis, both active and arrested, is the most frequent cause of massive hemoptysis[41,42] and together with bronchiectasis,[29,42] pulmonary abscess[47,48] and aspergilloma[23] account for most cases.[49] Less common causes of massive hemoptysis include rupture of an aortic aneurysm into a bronchus, Goodpasture syndrome, systemic disorders associated with a bleeding tendency (such as leukemia), cystic fibrosis,[28] localized pulmonary bullae,[50] acquired[51] and congenital[52] heart disease, bronchial adenoma, and iatrogenic causes such as percutaneous or transbronchial lung biopsy, tracheal-innominate fistula due to tracheostomy, transtracheal aspiration and anticoagulation therapy. Although bronchogenic carcinoma is a cause of massive hemoptysis, bleeding in this disease is characteristically minimal but persistent.[2,4]

Massive hemoptysis treated nonsurgically has been associated with a high mortality rate.[41,42]

In one series 54 percent of patients who had hemoptysis of 600 ml or more in 48 hours and who were managed nonsurgically died; among patients who bled more than 600 ml in 16 hours mortality exceeded 75 percent.[41] In view of this high mortality rate in patients treated conservatively, an aggressive surgical approach has been advocated in the management of massive hemoptysis. In a nonrandomized study, Crocco reported 81 percent survival of 32 patients treated surgically compared with survival of only 1 of 9 (12 percent) patients treated nonsurgically.[41] Similar data favoring early thoractomy in patients with massive bleeding has been reported by others.[5,35,43,46,53]

Rigid bronchoscopy under topical anesthesia should be done in all patients with massive hemoptysis, occasionally even before less invasive diagnostic studies have been completed, since immediate endoscopic localization of the bleeding site is essential. The procedure should preferably be carried out in the operating room in case emergency thoracotomy is necessary. Although Bahabozorghi and co-workers felt that bronchoscopy was dangerous in patients with massive hemoptysis, and therefore recommended resecting the area shown to be abnormal on an x-ray film of the chest,[46] most other surgeons agree that inability to locate the bleeding site by endoscopy is a contraindication to surgery.[35,41,42,54]

If the bleeding site can be found, the endoscopist can attempt to control the hemorrhage through the bronchoscopic lumen by applying a sponge with dilute adrenalin or topical thrombin to the area of bleeding. If this is unsuccessful, the bronchus can be packed with sponges,[55] or a Fogarty catheter can be placed through the lumen of the rigid bronchoscope into the bleeding bronchus and the balloon inflated to tamponade the area.[56,57] Recently, this catheter has also been successfully passed into a bleeding bronchus through the suction channel of the fiberoptic bronchoscope.[58,59]

After the site of massive bleeding is identified, and a surgical approach decided upon, the patient should be anesthetized and intubated in preparation for emergency thoracotomy. Although a double-lumen Carlens endotracheal tube has been designed to prevent blood spreading from one lung to the other, its use is no longer recommended because of the expertise required for its insertion and because of its small lumen.[46,53,56] A large bore endotracheal tube is more effective because it is better for aspirating blood clots and can be placed in the mainstem bronchus of the nonbleeding lung to protect that lung from further aspiration of blood during the operation.[5,54]

Not all patients with massive hemoptysis can be managed surgically. A patient with severe chronic obstructive pulmonary disease or far advanced cavitary tuberculosis may not have enough pulmonary reserve to survive a surgical procedure or may end up a respiratory cripple. Many criteria based on pulmonary function studies have been proposed for evaluating the risk of pulmonary resection. However, pulmonary function studies including simple spirometry may be difficult or impossible to carry out in patients with unrelenting hemoptysis. Furthermore, the validity of criteria used to exclude patients as surgical candidates is questionable following recent aspiration of large amounts of blood.

There are occasional cases of massive hemoptysis that are best treated by modalities other than pulmonary resection. Examples include massive hemoptysis due to mitral stenosis which should be treated by mitral commisurotomy or valve replacement;[51] pulmonary hemorrhage due to a bleeding disorder where therapy should be directed toward correction of the bleeding tendency when possible; the diffuse bleeding of Goodpasture syndrome which cannot be treated by localized surgical resection but which may respond to high dose steroids[60] or bilateral nephrectomy.[61] Finally, in patients with metastatic bronchogenic carcinoma surgical therapy for massive hemoptysis generally should not be carried out because of the very poor prognosis.[41,54]

Patients with massive hemoptysis who are not surgical candidates, such as those in whom the site of bleeding has not yet been identified, should be placed in a critical care unit and receive the following intensive medical management:

- Most important is the maintenance of the airway which may necessitate intubation or rigid bronchoscopy to suction blood.
- Proper positioning of the patient including slight Trendelenberg position to promote drainage, and the lateral decubitus position with bleeding side down (if known) to decrease the amount of blood spillage into the normal lung.
- Arterial blood gas studies as a guide to oxygen therapy and need for assisted ventilation.
- Small doses of sedatives to decrease anxiety; cough depressants such as codeine are contraindicated.

- Platelet count and coagulation studies; specific replacement therapy when possible.
- Serial hematocrits to determine need for transfusion.
- Bronchodilators for patients with chronic obstructive pulmonary disease to improve reversible airway narrowing; intermittent positive pressure devices to deliver bronchodilators should be avoided.

When an adequate airway and acceptable oxygen tension cannot be maintained because of massive pulmonary hemorrhage in a patient who is not a surgical candidate, extracorporeal membrane oxygenation should be considered in select cases. This procedure recently proved lifesaving in a patient with massive hemoptysis due to Goodpasture syndrome.[62]

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Specialty Conference

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Acute Renal Failure

STANLEY A. MENDOZA:* Children with acute renal failure are gravely ill but in most cases can recover completely. Good medical management can make the difference between survival with complete recovery and death of the child. I plan to emphasize the treatment of children with acute renal failure. However, I will begin with definition of acute renal failure, followed by a discussion of its causes, incidence and prognosis.

Acute renal failure is the sudden, progressive loss of renal function. Oliguria is common in children with acute renal failure, but it is not always present. There are a number of children who present with virtually complete loss of renal function but with a sizable urine output.

There are prerenal, renal and postrenal causes of acute renal failure. Gastroenteritis is the most common of the prerenal causes. Children with this condition respond well to treatment in virtually all cases. Other prerenal causes of acute renal failure are burns, hemorrhages, hypotension and renal artery obstruction.

There are a number of parenchymal renal diseases that can cause acute renal failure. The three most common are acute poststreptococcal glomerulonephritis, hemolytic uremic syndrome and acute tubular necrosis. At one time the most common renal parenchymal disease that caused acute renal failure in children was poststreptococcal acute glomerulonephritis. This is no longer true, at least in the area of our institution. There is no obvious explanation for this trend. There are many children with streptococcal infections. In addition, in a significant number of children acute poststreptococcal glomerulonephritis develops, although in perhaps fewer than in the past. However, the disease is usually milder than in the past, and it is unusual to see a child with severe acute renal failure from poststreptococcal glomerulonephritis.

Hemolytic uremic syndrome (HUS) is a condition that usually begins with bloody diarrhea. Three days to a week later, extreme pallor and acute renal failure suddenly develop, usually associated with anuria and thrombocytopenia. There is a significant geographic variation in the severity of this syndrome. In California, 80 to 90 percent of the children with HUS recover completely.[1,2] These children are often hypertensive and may be anuric for periods of up to three weeks, but they usually recover completely. HUS was first described in 1955.[3] Until dialysis become generally available, a child with severe acute renal failure due to HUS would almost certainly have died. Consequently, the longest follow-up in these children is 10 to 12 years. During that time, the children who have apparently recovered completely from their acute illness have remained well. It seems likely that these children do not have residual damage to the kidneys, but there is no way to be sure that chronic renal disease will not evolve later.

Patients with poor renal perfusion due to dehydration, burns, hemorrhage or hypotension have a condition which can be immediately reversed if renal perfusion is improved. If the hypoperfusion of the kidney continues long enough, there can be parenchymal damage and acute tubular necrosis (ATN). This is probably the most com-

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ABBREVIATIONS USED IN TEXT

ASO = antistreptolysin-O
ATN = acute tubular necrosis
GFR = glomerular filtration rate
HUS = hemolytic uremic syndrome

TABLE 1.—*Potentially Lethal Complications of Acute Renal Failure*

- Circulatory overload
- Hypertensive encephalopathy
- Hyperkalemia
- Uremia
- Infection

mon of the causes of acute renal failure in children, particularly in intensive care nurseries, where infants are frequently hypoxic and hypotensive for varying periods of time. If that period is sufficiently long, ATN develops. This is also a potentially reversible disease.

Of the postrenal causes of acute renal failure, the most common is obstructive uropathy. If the diagnosis is made early enough, there is a potential for complete or nearly complete recovery of renal function unless the obstruction is associated with renal dysplasia.

The most common causes of acute renal failure, therefore, are dehydration, acute poststreptococcal glomerulonephritis, hemolytic uremic syndrome, acute tubular necrosis and obstructive uropathy. Each has a good prognosis if the child is treated properly during the acute illness. There is no specific treatment for the parenchymal causes of acute renal failure, acute tubular necrosis, hemolytic uremic syndrome or acute poststreptococcal glomerulonephritis. Basically, what must be done is to support the patient until he recovers spontaneously. The treatment of these children is designed to prevent or reverse the potentially lethal complications of acute renal failure. These are listed in Table 1. I shall discuss the cause, prevention and treatment of each of these complications.

Circulatory overload in children with acute renal failure results from the retention of salt and water. The diseased kidney is unable to maintain homeostasis. If salt and water overload are prevented in a child with acute renal failure, the signs of circulatory overload will not develop. Thus, prevention of circulatory overload is really quite simple. The patient should be given no salt and very little water. The implication of this statement is that acute renal failure is usually not associated with intrinsic cardiac disease.

Existing circulatory overload is difficult to treat. These children may present with a gallop rhythm, pulmonary edema, cardiomegaly, hepatomegaly and peripheral edema. Classical methods of treating congestive heart failure such as phlebotomy, rotating tourniquets, use of oxygen, bed rest, elevating the bed and morphine administration should be used.

It must be emphasized that digitalis is contraindicated. In these patients, the load on the heart progressively increases due to salt and water retention. The heart responds to this increased load by increasing contractility in accordance with Starling's law. Cardiac contractility increases until the load gets so great that a further increase in contractility is impossible and circulatory overload results. Digitalis acts by increasing cardiac contractility. Since the heart is incapable of further increasing contractility, digitalis is ineffective. Thus, one reason not to use digitalis is that it does not work. Digitalis has, in fact, been given to a large number of patients with acute renal failure and circulatory overload. It is usually ineffective. The major reason for not using digitalis, however, is that it is extremely dangerous. Digitalis is mainly excreted by the kidney. Therefore, it is easy to produce digitalis intoxication in a patient with impaired renal function. Furthermore, management of digitalis intoxication in a patient with acute renal failure is extremely difficult. The usual treatment for digitalis intoxication is intravenous administration of potassium, which is extremely dangerous in a child with renal dysfunction. In addition, digitalis is not dialyzable, so that if a patient becomes digitalis intoxicated the drug can not be easily removed. In fact, dialysis tends to make the digitalis intoxication worse because potassium is removed by dialysis, thereby potentiating the effect of digitalis. I have seen two children in whom severe arrhythmias developed after the use of digitalis in acute renal failure. I feel very strongly that it is contraindicated in almost all cases. The exceptions to this rule are the patients who have acute renal failure and intrinsic cardiac disease. In these cases, digitalis may be indicated because it can improve cardiac contractility. In such cases, digitalis should be administered extremely carefully with frequent electrocardiograms and measurement of blood levels of digitalis.

Diuretics are frequently ineffective in patients with acute renal failure due to parenchymal renal disease. Diuretics act by decreasing the sodium chloride reabsorptive capacity of some part of the nephron. Thus, more sodium chloride and water are excreted. Patients with severe acute renal failure due to parenchymal renal disease may have a very low glomerular filtration rate (GFR). Obviously, if the GFR is sufficiently low, decreasing tubular reabsorption will not increase urinary sodium and water excretion. Consequently, many patients with acute renal failure do not respond to diuretics. However, some patients with acute renal failure and circulatory overload do respond well to a diuretic such as ethacrynic acid or furosemide. Even a small diuresis can be sufficient to make a dramatic difference in the clinical course of a patient with circulatory overload. The heart rate slows, the gallop rhythm disappears and oxygenation improves. Of course, this is the reason that phlebotomy is a part of standard therapy. Phlebotomy is another way to remove volume acutely from the plasma. Ethacrynic acid or furosemide is indicated in children with acute renal failure and circulatory overload. In a normal person each may cause the excretion of as much as 20 percent of the filtered sodium. Side effects are minimal. Both of these drugs can cause deafness. In the case of furosemide, I am unaware of irreversible deafness. There are reports of irreversible deafness due to use of ethacrynic acid.[4] The major reported side effect of both ethacrynic acid and furosemide is imbalance of fluid and electrolytes caused by excessive loss of water and salt. In a child with severe circulatory overload and acute renal failure, it would be delightful to have to worry about replacing excessive salt and water loss. Since these diuretics occasionally work dramatically and are relatively innocuous, they should be tried.

Peritoneal dialysis or hemodialysis is quite effective in treating patients with acute renal failure and circulatory overload. In practical terms, it takes one to two hours to start an emergency peritoneal dialysis or to arrange surgical vascular access before hemodialysis. In a child with acute renal failure, and circulatory overload, I start with phlebotomy, rotating tourniquets, oxygen, diuretics and morphine, but at the same time, I begin organizing emergency dialysis. In one to two hours when the dialysis can begin, the patient will either have improved significantly with conservative management or not. If he has, conservative management can be continued without dialysis. If he has not improved significantly, then dialysis can begin immediately.

A second potentially lethal complication of acute renal failure is hypertensive encephalopathy. There are several causes of hypertension in patients with acute renal failure. The most significant cause is retention of salt and water. If retention of salt and water are prevented, hypertension will usually not be severe. Renal vascular disease can also occur with impairment of renal perfusion. This can result in the release of renin by the kidney. Renin then causes a protein in the blood to be converted to angiotensin I and II. Angiotensin II is an extremely powerful pressor agent. The renal parenchymal causes of renal acute failure can increase plasma renin activity.

A child we saw recently was of particular interest because he presented in an unusual manner, with an acute onset of blindness. His eyegrounds were normal initially but his blood pressure was 220/160 mm of mercury. An EMI® scan done early in the course of the illness showed a decrease in perfusion to the occiput, where the visual cortex is located. When the abnormal blood pressure was adequately treated, his vision returned. We thought he had hypertensive encephalopathy localized to the occiput. On the third hospital day his blood pressure rose again, and during this rise the patient again became blind. Fortunately when hypertension was treated, vision returned, and he is now perfectly normal. This boy had acute poststreptococcal glomerulonephritis with abnormal findings on urinalysis, an elevated antistreptolysin-O (ASO) titer and low serum complement. Another child with acute poststreptococcal glomerulonephritis presented with a generalized seizure. His blood pressure was 240/180 mm of mercury, and he had florid hypertensive retinopathy. He did well after receiving antihypertensive therapy.

Severe hypertension is life-threatening. In patients with acute renal failure, severe hypertension can usually be prevented by careful monitoring of the intake of salt and water. Antihypertensive drugs are indicated. When the blood pressure is notably elevated a parenteral agent which acts rapidly is indicated. In general the initial drug of choice is hydralazine. When given intravenously, this drug acts rapidly and can be repeated every 15 minutes until the blood pressure falls.

In a true hypertensive emergency even hydralazine may act too slowly. In such a case the

best drugs are diazoxide and nitroprusside. Diazoxide is given by rapid intravenous injection in a dose of 2 to 5 mg per kg of body weight. The blood pressure usually falls rapidly after diazoxide administration. An effect is generally seen within five minutes, often in one to two minutes. One dose is usually effective for 6 to 12 hours, and the drug can be repeated. Nitroprusside is given by intravenous drip. The infustion rate is slowly increased until the blood pressure falls. One problem with nitroprusside is that it is unstable in light. For this reason, the IV bottle and tubing must be wrapped in a light resistant material such as aluminum foil. When diazoxide or nitroprusside is used, it is important to begin oral antihypertensive therapy at the same time to provide long-term control of blood pressure. Dialysis can be used to treat hypertension in acute renal failure since salt and water overload is a major cause of the hypertension. In a severe hypertensive emergency, dialysis is too slow. As mentioned earlier, it usually takes one or two hours to start the dialysis. Another one or two hours pass before the dialysis significantly affects the blood pressure. Therefore, the initial treatment is with antihypertensive drugs. Dialysis can be useful in keeping the blood pressure down.

A third cause of death in patients with acute renal failure is electrolyte imbalance, especially hyperkalemia. Although these patients can have acidosis, hypocalcemia, hyperphosphatemia, hyponatremia or hypernatremia, the major life-threatening change in serum electrolytes is an elevation in the serum concentration of potassium. Hyperkalemia in patients with acute renal failure is caused by dietary intake of potassium and tissue breakdown. These patients are seriously ill and are catabolic. As tissue is broken down, large amounts of potassium are released because intracellular concentrations of potassium are high. Another cause of hyperkalemia is the administration of blood, particularly old blood. When blood is stored, the potassium from the red cells leaks into the plasma. The plasma potassium concentration of such blood can be 15 to 20 mEq per liter. In addition some patients with acute renal failure, especially those with HUS, have significant hemolysis releasing potassium into the plasma.

Hyperkalemia can be prevented in several ways. First the patient with acute renal failure needs absolutely no potassium intake. The most significant route by which the body loses electrolytes is the urine. If a patient is anuric, electrolyte losses are minimal. In anuric patients the major problems with electrolytes occur when too much is given. Thus too much sodium causes circulatory overload and hypertension. Too much potassium causes dangerous hyperkalemia. It is difficult to give too little sodium or potassium to an anuric patient. Second, caloric intake should be encouraged. If 20 to 25 percent of the daily calorie requirements are taken, either as carbohydrate or fat, protein catabolism is decreased, thus decreasing the release of potassium from cells. This also slows the rate of increase in the blood urea nitrogen. Third, only fresh blood should be given. The serum potassium concentration in fresh blood is low. Further, packed cells should be infused since this decreases the volume of potassium-containing plasma administered as well as decreasing the total volume infused, thereby decreasing the risk of producing circulatory overload or severe hypertension. If a transfusion is necessary, only buffy coat poor or frozen red cells should be used. Although most such patients recover, some do not. Therefore, any patient with acute renal failure should be regarded as a potential candidate for a renal transplant. Buffy coat poor or frozen red cells significantly decrease the risk of sensitizing the patient to foreign antigens.

TABLE 2.—*Methods of Treating Hyperkalemia*

Agent	*Onset of Effect*	*Duration of Effect*
Calcium gluconate	< 5 minutes	30-60 minutes
Sodium bicarbonate	< 5 minutes	1-2 hours
Insulin and glucose	20-30 minutes	2-4 hours
Kayexalate	1-2 hours	4-6 hours
Dialysis	Variable	Variable

Table 2 lists methods of treating hyperkalemia in order of their onset and duration of action. Calcium and sodium bicarbonate work extremely rapidly. The electrocardiographic changes of hyperkalemia improve dramatically in one to two minutes. Calcium acts by antagonizing the effects of potassium on cardiac muscle. Bicarbonate acts by releasing hydrogen ions from the cells in exchange for potassium ions. Neither calcium nor bicarbonate removes potassium from the body in a patient with renal failure. Therefore, their effects tend to be brief, usually lasting about one hour. Since calcium and bicarbonate are short acting, their use is only indicated in a patient with an arrhythmia due to severe hyperkalemia. If the patient has a high serum potassium concentration and peaked T waves but no arrhythmia, insulin and glucose may be given. Insulin causes

the uptake of glucose by muscle cells. Potassium is taken up with the glucose. Therefore, insulin and glucose remove potassium from the plasma, thereby improving the patient's general status, but do not remove potassium from the body. It is generally stated that it takes 20 to 30 minutes for insulin and glucose to work, but I have seen improvement on electrocardiograms in less than five minutes after insulin and glucose administration.

The two forms of therapy for hyperkalemia which remove potassium from the body are the ion-exchange resin, polystyrene sulfonate (Kayexalate®) and dialysis. Kayexalate is given either orally or rectally in the sodium form. The affinity of the resin is higher for potassium than for sodium. Sodium is exchanged for potassium and the potassium-containing resin is excreted in the stools. One potential complication of Kayexalate therapy is that for each potassium ion removed from the body, one sodium ion is added. This can cause salt and water overload while the hyperkalemia is improving. Dialysis is an extremely effective way of removing potassium from these patients.

The fourth cause of death in acute renal failure is uremia. The uremic syndrome includes many problems but the life-threatening complications are neurologic, including lethargy, coma and seizures. There is a great deal of debate in the literature as to the nature of the uremic toxin or toxins. There are a number of complications of uremia including peripheral neuropathy, pericarditis, neurologic symptoms, myopathy and others. It is not clear whether a single toxin causes all of these complications, or if there is a different toxin for each. It is generally assumed that the toxin or toxins are tissue breakdown products, possibly nitrogen-containing tissue breakdown products but even this is unproven. The onset of uremic symptoms can apparently be delayed by minimizing tissue breakdown by giving adequate calories. Dialysis will treat or prevent the neurological complications of acute renal failure. Presumably some toxin or toxins are removed by dialysis.

The fifth cause of death in acute renal failure is infection. In some series of adults, infection was the most common cause of death in patients with acute renal failure. Uremic patients have decreased resistance to infection because of defects in both humoral and cellular immunity. A second cause of infection is that these patients are often lethargic or comatose. They tend to lie flat in bed and decubitus ulcers, hypostatic pneumonia or other opportunistic infections which occur in severely ill patients can develop. This risk can be minimized by excellent nursing care with appropriate turning of patients and respiratory therapy. A third cause of infection in these patients is the use of indwelling urinary catheters. The only information that an indwelling catheter provides is an hour-by-hour measure of urine output. This information is therapeutically worthless. It is clinically relevant to know if urine output is high or low. This information is available without using an indwelling catheter since if urine output is high the patient will either void or develop a full bladder. An indwelling urinary catheter is particularly dangerous in patients with a low urinary output. A patient with an indwelling urinary catheter and a high urine volume may wash out bacteria which enter the bladder. If urine output is low, the bacteria which enter the bladder multiply without significant washout. Therefore, the use of an indwelling urinary catheter should be avoided. There is an occasional reason for an in-and-out bladder catheterization to determine urine output or to obtain urine for culture. This is an essentially benign procedure if done carefully. Indwelling catheters are not benign.

TABLE 3.—*Therapy for Oliguric Patients*

- Water—calculated insensible loss plus urine output.
- Sodium—replacement of urinary loss.
- Potassium—none
- Calories—at least 20 to 25% of daily requirement, as carbohydrate and/or fat.

A high index of suspicion is necessary to recognize infection. If infection is suspected, antibiotics should be given after appropriate cultures are obtained. Since many antibiotics are nephrotoxic or excreted by the kidney, or both, modification of dosage schedules may be necessary.

Table 3 is a proposed treatment regimen for oliguric patients. Recommended fluid intake is insensible loss plus the urine output. If the patient is initially somewhat volume overloaded, he should be given less fluid than this so that total levels of body water will return to normal. Virtually all fluid volume problems in patients with acute renal failure are due to volume overload. Therefore, if there is any question about the volume of fluid to be given, the smaller volume should be used.

TABLE 4.—*Indications for Dialysis in Acute Renal Failure*

- Severe circulatory overload
- Severe hypertension
- Hyperkalemia
- Uremic symptoms

Sodium losses can be estimated by measuring urine volume and urinary sodium concentrations unless the patient has either cystic fibrosis with a high salt concentration in the sweat or gastrointestinal losses. Most problems result from giving too much sodium. No sodium should be given to anuric patients. Urinary potassium excretion can be monitored and potassium loss replaced. Here again, patients with acute renal failure are more likely to have problems with potassium overload than with potassium depletion. At least 20 to 25 percent of the estimated caloric requirements should be given as carbohydrates or fats.

Table 4 lists the indications for dialysis in acute renal failure. The resemblance between this list and the listing in Table 1 of the causes of death in patients with acute renal failure is intentional. The indication for dialysis in these patients is any complication of uremia which is unresponsive to conservative management.

If one treats a patient with acute renal failure appropriately and does dialysis when indicated, the chance of the patient surviving the acute illness is very high. If the acute illness is ATN, HUS or acute poststreptococcal glomerulonephritis, the probability is extremely high, perhaps 80 to 90 percent, that this recovery will be complete.

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Cholecystitis in Patients with Diabetes

The occurrence of acute cholecystitis in patients with diabetes deserves special mention. In the presence of diabetes, perforation of the gallbladder is more frequent, and it often occurs within 72 hours of the onset of the disease. Most important, the mortality rate of acute cholecystitis in those with diabetes is high: it ranges from 8 percent to 22 percent. For these reasons, there really is no place for nonoperative treatment. In patients with diabetes, an operation should be undertaken with dispatch as soon as the diagnosis is made.

—MARSHALL J. ORLOFF, MD, *San Diego*

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Refer to: Total parenteral nutrition—State of the art—Medical Staff Conference, University of California, San Francisco. West J Med 127:397-403, Nov 1977

Total Parenteral Nutrition—State of the Art

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and Robert C. Siegel, Associate Professor of Medicine and Orthopaedic Surgery, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *I think that most people would agree that nutrition is one of the topics we neglect in most of our presentations. Today, Medical Grand Rounds will be devoted to an important topic in nutrition: hyperalimentation. Dr. Janet Abrahm will present the case summary.*

Case Summary

DR. ABRAHM:† The patient is a 24-year-old man with mixed embryonal testicular cancer in relapse with metastasis to retroperitoneal nodes, lung and liver, for which he had received several courses of chemotherapy before this admission.

On physical examination at this admission, blood pressure was 95/65 mm of mercury and pulse 82; these values changed to 90/60 mm of mercury with a pulse of 102 when the patient stood up. Weight was 81.6 pounds (37 kg). Findings on examination of head, eyes, ears, nose, throat, skin, lungs and heart were all unremarkable. On examination of the abdomen, the liver was found to be enlarged. Rectal examination showed a trace positive stool guaiac. Genitourinary examination showed the left testicle to be absent. Reflexes were 0 to 1+, symmetrical, and no Babinski reflexes were present. The admission prothrombin time was 14.8 seconds. The patient was vomiting on admission and there was a question of a gastric outlet obstruction. It was felt necessary to give chemotherapy courses and to provide adequate nutrition. Therefore, hyperalimentation was begun. For the tumor, two courses of cyclophosphamide (Cytoxan®), adriamycin and cystplatium were administered. This treatment resulted in a decrease in the size of the lung lesions and virtual resolution of the obstruction to gastric overflow.

Administration was begun of a hyperalimentation solution (Travasol®) with 25 percent dextrose and appropriate concentrations of sodium, potassium, chloride, phosphate, magnesium and calcium. Folate was added biweekly; multivitamins and trace elements, including zinc, copper, cobalt, manganese and potassium iodine were administered daily. Topical safflower oil, which is 85 percent linoleic acid, was added during the sixth week because a greasy, brownish, scaling lesion of the eye margins, lids and nose developed, consistent with a deficiency of essential fatty acids or zinc. Zinc level at that time was 16 μg per ml (normal 55 to 150). The patient has gained 30 pounds while receiving hyperalimentation, dermatitis has resolved and hyperalimentation is now being decreased.

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*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine.

†Janet Abrahm, MD, Chief Resident.

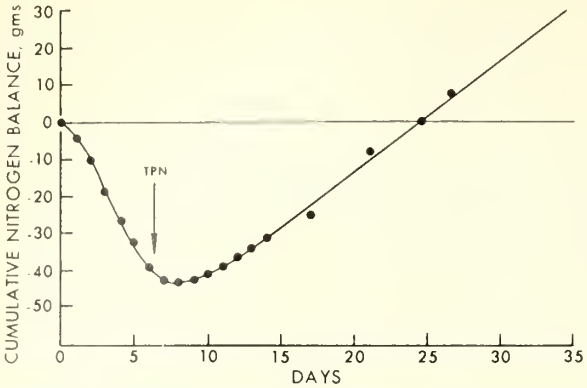

Figure 1.—Nitrogen balance studies performed during total parenteral nutrition in a patient with regional enteritis. Administration of hypertonic dextrose and amino acids was associated with reversal of catabolism. TPN = Total parenteral nutrition.

DR. SMITH: *Thank you, Dr. Abrahm. We are extremely pleased to have Dr. George Sheldon to discuss this case and particularly to discuss the whole process of hyperalimentation and developments in the field.*

DR. SHELDON:* Thank you, Dr. Smith. It is a pleasure to participate in Medical Grand Rounds. I had the opportunity to see this patient during his hospital stay. There were several things that should be commented on in his care. First, we usually provide vitamins and trace metals from the outset to prevent depletion. Also, we have a protocol for administering fat regularly so that the disorder seen in this patient, essential fatty acid deficiency, does not occur.

The capability of providing sufficient calories, protein, fat and other nutrients intravenously to maintain growth, development and weight has been a clinical reality for ten years. Total parenteral nutrition has evolved into a clinical subspecialty, as evidenced by the recent founding of a society (American Society for Parenteral and Enteral Nutrition [ASPEN]) and a journal (*J-PEN* [*Journal of Parenteral and Enteral Nutrition*]) which deals entirely with nutritional support. Moreover, recommendations are pending that would require hospitals using complex methods of nutritional support such as total parenteral nutrition to structure a team charged with its safe implementation.

Recent advances have occurred in many aspects of hyperalimentation.[1-3] Efforts to quantify accurately the nutritional status of patients and to gauge the need and response to nutritional support have evolved. Bistrian and Blackburn have advocated use of a creatinine-height index, patterned after that of the World Health Organization. Published tables serve as standards for calculating the patient's ideal creatinine-height index and serve as an estimate of lean body mass. Since muscle mass is an important source of amino acids which can be recycled to support visceral proteins and maintain blood sugar through gluconeogenesis, a noninvasive nutritional assessment profile is a valuable clinical tool. Utilization of the World Health Organization standards for midarm muscle circumference is a simple assessment carried out with a tape measure, which provides an estimation of muscle protein status, also. A skin caliper can be used to measure the triceps skin fold; this provides an assessment of body fat composition.

Nitrogen balance is a time-honored measurement of the dynamics of nutritional depletion and repletion. Nitrogen balance reflects muscle degradation which through gluconeogenesis liberates nitrogen to be excreted primarily as urinary urea. A reasonable approximation of protein catabolism can be obtained by measuring daily levels of urea nitrogen in urine. When the excreted urea nitrogen is subtracted from the administered protein nitrogen, a reasonable approximation of balance is obtained (Figure 1).

Current investigations in our and other laboratories are focusing on the assessment of proteins of visceral origin, such as albumin and transferrin, and immunocompetence in addition to nitrogen balance.[4,5] "Visceral proteins" such as serum albumin are sensitive indicators of prolonged protein depletion. As the biological half-life of albumin is 20 days, a patient with hypoalbuminemia (less than 3.4 mg per 100 ml) obviously has significant protein depletion. Other "visceral proteins" such as those responsible for humoral immunity, erythropoietin and transferrin have significantly shorter half-lives than albumin. If hypoalbuminemia is present, the other "visceral proteins" are predictably more depleted. As malnourished patients usually die of sepsis and pneumonia, loss of muscle strength and diminished immunocompetence are perhaps more relevant assessment measures than nitrogen balance. Serum albumin, the weight-height index, transferrin levels, and urea balance should be followed in all patients in hospital with prolonged illness who are receiving nutritional support.

*George F. Sheldon, MD, Associate Professor of Surgery, University of California, Chief of Trauma and Hyperalimentation Services, San Francisco General Hospital.

TABLE 1.—*Indications for Nutritional Support*

- Anatomic or functional loss of gastrointestinal integrity
- Hypermetabolism
- Albumin less than 3.4 mg per 100 ml
- Prophylactic—"five-day rule" (see text)
- Multiple organ system failure: renal failure, hepatic failure, cardiorespiratory failure

In addition to laboratory tests, bedside assessment is essential. A recent operation, thermal injury or febrile illness will expend considerable calories and protein. In addition to the 1,800 calories needed for basic maintenance, 1°F of body temperature elevation will increase daily caloric expenditure by 500 to 700 kilocalories. Part of the bedside assessment is application of the so-called "five-day rule." If after five days of food deprivation it seems likely that oral feeding will occur within two additional days, no specific nutritional support is usually required. If the assessment is to the contrary, implementation of nutritional support by tube feeding, special diets or parenteral nutrition should be initiated to prevent further wasting of body cell mass (Table 1).

In addition to nutritional assessment, progress has occurred in access routes for parenteral feeding. Subclavian vein catheterization, popularized by Dudrick in 1967, remains the preferred route for administration of a hyperosmolar solution. However, subclavian vein thrombosis will occur in some patients in whom long-term intravenous feeding is required. Although single subclavian vein thrombosis is usually not a clinical problem, access for parenteral feeding is lost if it is bilateral. For that reason we frequently use a silastic catheter (Broviac catheter) which is inserted through a subcutaneous tunnel by way of the cephalic vein into the right atrium when prolonged intravenous feeding is anticipated. The Broviac catheter was developed for patients in whom home hyperalimentation is required and has been referred to as the "artificial gut."[6] This method of access is useful in patients who have lost much of the absorptive surface of the small intestine and is valuable in patients who have tracheostomy, because it allows the catheter exit site to be distant from the potential sepsis of the tracheostomy.

The capability for providing long-term total intravenous feeding out of the hospital was pioneered by Dr. Belding Scribner at the University of Washington. Unlike home hemodialysis for renal failure, many patients receiving home hyperalimentation are able to return to enteric feeding. Currently more than 150 patients in the United States with anatomical or functional loss of gastrointestinal integrity are benefiting from this mode of therapy; our home hyperalimentation unit at San Francisco General Hospital is becoming increasingly busy.*

Starvation, Stress and Body Composition

Rational use of hyperalimentation requires knowledge of body composition. In an idealized 70 kg (154 pound) man, 15 percent of the body weight is in the form of protein, less than 2 percent of the body is in the form of glycogen, and the variable fat mass may range from 9 percent to 50 percent of total body composition. In the structure of these basic components are potential interconvertible energy sources. Maintenance of blood sugar levels occurs by catabolism of muscle and subsequent formation of glucose by the process of gluconeogenesis. During a period of brief starvation, 10 to 15 grams of nitrogen will be excreted in the urine daily, representing catabolism of protein to fulfill energy requirements.[7] After several days of food deprivation, lipolysis of fat begins to be a significant source of energy. Starvation adaptation, during which the body shifts from a protein source for energy to one of fat, is well established by two weeks of food deprivation. After 14 days of food deprivation, minimal amounts of nitrogen (<2.0 gms) are excreted daily and ketosis is present, indicating primary support of metabolic functions by fat. The shift from protein to fat as an energy source is associated with a reduction in urea synthesis and excretion, and in free water clearance. It is also associated with a low metabolic rate, decreased activity, and decreased serum insulin values. During starvation adaptation, the brain and heart utilize "ketone bodies" for energy substrate. Fat adaptation allows considerable time (over two months) to pass before death from starvation occurs.

In contrast to starvation, a patient with an illness characterized by increased catecholamine levels will have a high metabolic rate, a relatively fixed rate of muscle protein catabolism and will not adapt to the utilization of lipid substrates to provide energy needs. Such patients, whether their illnesses are medical, surgical or pediatric, can lose up to 30 percent of their lean body mass in one month if nutritional support is not provided. Although protein can be degraded

*A home hyperalimentation registry has been established by the American College of Surgeons.

TABLE 2.—*Hypertonic Intravenous Nutrition, Requiring Central Venous Access*

Hyperalimentation meets requirements of
Calorie, protein, lipid
Electrolyte, vitamins, micronutrient
Calorie:nitrogen ratio—150:1
Hypertonic, hyperosmolar requiring central vein
Metabolic rather than gut substitute
Renal failure
Hepatic encephalopathy—special amino acid
Hypermetabolism—increased nutrients
Pediatrics—less glucose, more fat and amino acids

for the maintenance of important energy functions, body structure is lost when protein becomes the primary source of energy substrate. This is comparable to "burning the front porch to keep a fire going." The patient who is in addition deprived of food, although adapted to sparing of protein by fat, will continue to lose significant protein throughout the entire course of his or her period of nutritional deprivation.

In critically ill patients with multiple organ failure (renal failure, hepatic failure, respiratory failure), parenteral nutrition is begun as soon as the patient is hemodynamically stable. Aggressive nutritional support is an obligatory form of management to meet the increased substrate requirements and metabolic needs of catastrophically ill patients.

Techniques of Intravenous Nutritional Support

Two basic methods for providing intravenous nutrition are currently popular and involve hypercaloric or hypocaloric regimens. Total parenteral nutrition (hyperalimentation) should meet the requirements for calories, protein, vitamins, electrolytes, minerals, macronutrients and fat (Table 2). As hyperalimentation is hypertonic and hyperosmolar, it requires a central venous access route into an area with rapid blood flow. It has a calorie-to-nitrogen ratio of approximately 150:1 and the calorie source is concentrated dextrose. Micronutrients, macronutrients and vitamins are provided to meet recommended daily requirements as well as special needs. The standard solutions assume adequate renal function to clear the free water and urea produced by the metabolism of these substances. Standard hyperalimentation basically serves as a gut substitute and requires adjustment based on nitrogen balance and the other assessment measures of efficacy.

For some patients the need for hypertonic intravenous feeding is a metabolic one rather than substitution for inadequate gastrointestinal tract function. In patients with disorders of nitrogen metabolism such as renal or hepatic failure, individual determinations of calorie and protein needs are essential because of the inability of such patients to utilize nutrients appropriately or excrete end products of protein metabolism. In patients with acute renal failure who have high energy needs, insulin resistance and inability to clear free water with urea, the parenteral feeding has special objectives. Patients with renal failure require a very hypertonic solution with a calorie-nitrogen ratio in excess of 450:1, and only about a third of the usual provision of protein in the form of amino acids. The objective of the therapy is to provide the maximal amount of calories with the minimal quantity of free water and nitrogen. When this regimen is effectively administered, gluconeogenesis is inhibited and blood urea and serum potassium levels are lowered. One study found improved survival in patients with acute tubular necrosis receiving dextrose and amino acids as compared with patients receiving hypertonic dextrose alone.[8]

Recently, with Dr. Fischer of Massachusetts General Hospital, we have begun testing a special amino acid mixture for use in patients with hepatic encephalopathy.[9] Patients with hepatic encephalopathy have decreased serum levels of branched chain amino acids and increased levels of aromatic amino acids. Provision of standard hyperalimentation solutions as well as orally given protein exacerbates this disturbance, which can be correlated with degree of hepatic encephalopathy. The solution developed by Dr. Fischer brings the plasma amino acids to normal levels, presumably rectifies abnormal neurotransmission and has been associated with improvement in hepatic encephalopathy in a small group of patients awakening from coma.

Targeting of special amino acid solutions to defined metabolic problems or diseases is an area of investigation being pursued actively by industry. In addition to renal and hepatic failure, cardiac cachexia is associated with lowered left ventricular stroke volume and filling pressures, both of which can be improved by aggressive nutritional therapy.

Patients with thermal injury or severe trauma frequently have a 150 percent increase in basal metabolic expenditure (BME) paralleling their degree of catabolism. Extensive thermal injury is associated with 40 to 50 grams of nitrogen loss

TABLE 3.—*Hypotonic Intravenous Nutrition, Administered Through Peripheral Vein*

"Protein Sparing" Therapy
Isonitrogenous, hypocaloric
Provides micronutrients and macronutrients and vitamins
Amino acids alone
Amino acids plus dextrose
Amino acids plus lipid
Indications
Intermediate between normal and intravenous alimentation
Morbid obesity
Fatty liver—total parenteral nutrition
Limitations
Weight loss continues
Blood urea nitrogen level rises
Hypoglycemia
Expense
No substitute for total parental nutrition or tube feeding

daily, a degree of protein breakdown which will be present until the burn is healed. Extensive injury may be associated with a loss of 30 percent of lean body mass in three to four weeks, unless aggressive nutritional intervention is employed.

Meeting nutritional needs by a hypocaloric isonitrogenous infusion which provides all nutrients except total calories is attractive because it can be administered through a peripheral vein (Table 3). Nitrogen balance can be improved by the peripheral infusion of amino acids in combination with intravenous fat.[10,11] Not only can nitrogen balance be improved by hypocaloric provision of amino acids, but albumin synthesis can be promoted by infusion of hypocaloric solutions.[12] The main problem with hypocaloric regimens is deciding when they should be used. Persons unfamiliar with hyperalimentation may, because of unfamiliarity with subclavian vein access routes, choose a hypocaloric routine for a patient who needs maximal nutritional support. Moreover, patients with brief illnesses or operations do not require any special nutritional support beyond the routine use of electrolytes and 5 percent dextrose solution.

Our current use of hypocaloric routines is confined to two groups of patients. The first group includes patients who are likely, but not certain, to resume oral nutrition within a week of food deprivation. Temporizing for a week with hypocaloric routines rather than initiating hypercaloric alimentation via the subclavian vein seems rational in such patients. Moreover, there are patients whose body decomposition is adequate but because of diagnostic tests and perhaps gastric obstruction may require up to a week of preparation for a surgical procedure and will benefit by maintaining protein integrity while they lose weight. Patients in whom hepatic steatosis develops from the long-term provision of hypertonic solutions of dextrose and protein should be treated intermittently with dextrose-free amino acids. This reduction in the amount of dextrose received will reverse the structural hepatic changes.

Solution Composition

The caloric base for parenteral nutrition is hypertonic dextrose. It is commercially available in concentrations of 70 percent, 50 percent or less. Hypertonic dextrose is added to a protein base to provide a usual infusion concentration of 25 to 30 percent dextrose. The maximal concentration which can be prepared, about 47 percent dextrose, is used in patients with large caloric requirements or when a high caloric density per unit volume is required such as in renal failure.

The other available caloric source is fat. A safe lipid emulsion (Intralipid®) containing the essential fatty acids in a soybean emulsion has been available for over one year. It is a 10 percent solution containing 1.1 calories per ml and is used twice a week to prevent essential fatty acid deficiency.

Many sources of protein are available. The whole proteins initially used, hydrolysates of casein or fibrin, are effective but are becoming less popular because of the quantity of nonutilizable nitrogen they contain. Synthetic amino acids are used frequently today because they meet recommended daily requirements for amino acids or the needs of special illnesses such as renal or hepatic failure. Until this past year only one amino acid solution (Freamine®) was on the market. At present, two additional amino acid solutions (Aminosyn®, Travamin®) have become available. There is little to choose among these products. Some solutions are premixed with electrolytes, which may limit flexibility in their use. Physicians must therefore be familiar with the products used in their hospitals.

Although electrolyte requirements must be individually tailored to each clinical situation, anabolism requires approximately 40 mEq of potassium and 20 mEq of phosphate for each 1,000 kilocalories infused (Table 4). Magnesium, sodium, trace metals such as copper, zinc, manganese and daily vitamin infusion are necessary also.[13] Vitamin K, folic acid, and vitamin B_{12} are not con-

TABLE 4.—*Electrolyte Requirements*

Sodium	As needed
Potassium	40 mEq per 1,000 kilocalories
Phosphate	20 mEq per 1,000 kilocalories
Calcium	35 mEq per 1,000 kilocalories
Magnesium	8 mEq per 1,000 kilocalories

tained in commercial multivitamin preparations and need to be added weekly or biweekly.

Mechanical, Septic and Metabolic Complications

Mechanical complications from placement of the subclavian catheter occur in less than 5 percent of patients.[14] Any structure, however, in the region of the subclavian vein (brachial plexus, lung, subclavian artery, thoracic duct) may be injured. The catheter may be inadvertently threaded into the jugular vein. Pneumothorax, however, remains the most common complication. Subclavian vein thrombosis secondary to prolonged administration of hypertonic solution is more common than thought. If subclavian vein thrombosis is bilateral, access for parenteral nutrition is difficult.

Sepsis is the most serious complication of hyperalimentation. Over the past five years, documented catheter sepsis rates have fallen from 30 percent to less than 3 percent in most units. Staphylococcus epidermis is the commonest organism associated with hyperalimentation catheter sepsis; candidiasis seldom occurs. Reduced rates of catheter sepsis are directly related to the formation of hyperalimentation teams, protocols and standardized practices. At San Francisco General Hospital, the sepsis rate between 1970 and 1972 was 28.6 percent. During the past year, the sepsis rate in more than 300 patients was less than 3 percent, with no patient requiring treatment of sepsis other than catheter removal.

Metabolic complications of the infused hyperalimentation solution relate to the substrate infused and deficiencies which develop. Complications of hypertonic dextrose infusion may occur when greater than 0.5 gm of glucose per kg of body weight is administered per 24 hours, if the patient has insufficient insulin (diabetes mellitus) to metabolize the sugar, or if insulin resistance (burn, uremia, sepsis, injury) is present. Hyperosmolar, nonketotic dehydration may occur within 12 hours in susceptible patients and has a mortality rate greater than 40 percent. It is treated by administration of insulin, but is best avoided by frequent analyses of urine and blood glucose. Many patients receiving parenteral nutrition will have blood glucose values of 175 to 200 mg per 100 ml. The addition of 10 to 15 units of regular insulin per each 1,000 dextrose calories is a useful practice. When a hyperalimentation solution is abruptly discontinued, hypoglycemia may occur. Gradual slowing of the infusion rate prevents this rebound hypoglycemia.

Metabolic complications secondary to the intermediary metabolism of protein are to some degree dependent on the product utilized. Fibrin hydrolysates have been associated with hyperammonemia. Hyperammonemia, however, can also occur when synthetic amino acids are administered, suggesting that higher concentrations of arginine than are currently present in commercially available solutions may be required. The first commercially available amino acid solution (Freamine) had the amino acids as chloride salts. With metabolism of these amino acid salts, hydrogen and chloride ions would be liberated with resultant metabolic acidosis. Current amino acid solutions are primarily acetate salts and seldom disturb acid base balance. Prerenal azotemia from infusion of protein solution may occur if the patient is dehydrated; if the calorie to nitrogen ratio is too low, or if the solution is administered too rapidly.

Essential fatty acid deficiency is frequently caused or exacerbated by hyperalimentation because intravenous dextrose infusions are associated with elevated serum insulin values and depressed lipolysis. Biochemical evidence of fatty acid deficiency may be detected within three days of initiating hyperalimentation. Fatty acid deficiency is diagnosed biochemically by an increase in the triene to tetraene ratio which is reflected as an elevation of 5,8,11 eicosatrienoic acid, a lipid which is usually undetectable in the serum (Figure 2). Essential fatty acids (linoleic acid, for example) are necessary for a variety of essential body functions, such as formation of prostaglandin-E, wound healing, immunocompetence and integrity of the skin. The clinical appearance of fatty acid deficiency is that of a flat, scaly dermatitis. Subcutaneous tissue structure is altered in advanced cases to give the axilla and groin a pachydermal appearance.

Hypophosphatemia is the most serious electrolyte abnormality associated with hyperalimentation.[15] It occurs within three days when phosphate-free hyperalimentation solutions are

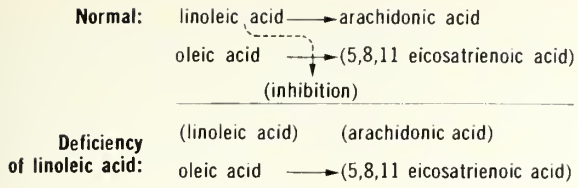

Figure 2.—Essential fatty acid deficiency. Because the essential fatty acid, arachidonic acid (tetraene), is formed from the essential fatty acid, linoleic acid, inadequate linoleate results in the deficiency of both of these essential fatty acids. When linoleic acid levels are low, 5,8,11 eicosatrienoic acid (triene) is formed from oleic acid stores. Linoleic acid normally inhibits the formation of 5,8,11 eicosatrienoic acid (triene) from oleic acid. In the deficiency of linoleic acid, 5,8,11 eicosatrienoic acid is formed and detectable. The broken lines depict regulatory effects, and the parentheses denote absent to minimal concentrations.

administered. Hypophosphatemia is associated with decreased serum phosphate and increased tubular reabsorption of phosphate, reflecting an extracellular to intracellular shift of phosphate ion. Because inorganic phosphate is a cofactor in the Emden-Myerhof pathway of glucose metabolism, hypophosphatemia causes low red cell values of 2,3 diphosphoglycerate (2,3 DPG) and adenosine triphosphate (ATP). Low values of 2,3 DPG and ATP result in increased hemoglobin affinity for oxygen and, when very severe, in hemolytic anemia.[16] Patients with hypophosphatemia may have high cardiac output, tachypnea and convulsions.

Trace metal deficiencies associated with long-term parenteral nutrition are being recognized with increasing frequency.[13] Copper deficiency, clinically apparent by refractory anemia, is common. Zinc deficiency, with impaired wound healing, was uncommon when the fibrin hydrolysates were the usual protein base. The increased use of amino acid solutions, if trace elements are omitted, is associated with low zinc values. Magnesium, manganese, iodine, as well as chromates, all should be added to the infusion when prolonged parenteral nutrition is anticipated.

Conclusion

Intravenous nutrition, called hyperalimentation by Dudrick and Wilmore[17] when first described, is among the most important advances in medical science of the past ten years. In addition to providing a simple method for nutritional support by a route other than the gastrointestinal tract, it has stimulated clinical and basic investigation in a neglected area of medicine, nutrition. Hyperalimentation, when provided by a team of health professionals (doctor, nurse, pharmacist, dietitian) can be safely administered for the benefit of patients treated by all disciplines of medicine.

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Important Advances in Clinical Medicine

Epitomes of Progress — Allergy

The Scientific Board of the California Medical Association presents the following inventory of items of progress in allergy. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in allergy which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Allergy of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Pulmonary Function in Asymptomatic Patients With Asthma

ABNORMALITIES in spirometric and lung volume measurements have been shown to occur in asthmatic patients during symptom free intervals. However, these measures may be within normal limits and still abnormalities may be found in measurement of small airways as well as in ventilation perfusion.

In patients completely asymptomatic by all clinical criteria, there may be decreased peak expiratory flow rate, decreased one second forced expiratory volume and decreased ratio of one second forced expiratory volume to vital capacity. Even when results of these tests have returned to normal along with airway resistance and specific airway conductance, measurements of residual volume, functional residual capacity, and the ratio of residual volume to total lung capacity may remain abnormally large.

Local areas of small airway dysfunction may continue to be present in asymptomatic patients, causing early closure of these airways. This is reflected in frequency dependence of compliance, an increased slope of the alveolar plateau and high closing volumes measured by the single breath gas dilution technique. Closing volumes may, in fact, be greater than functional residual capacity so that airway closure occurs during tidal ventilation.

Overall hyperventilation is known to occur in asthmatic patients with local areas of hypoventilation and hypoperfusion. The ventilation defects, however, have been shown to be of greater severity than the perfusion defects, resulting in ventilation perfusion mismatching. Ventilation perfusion defects with generalized hyperventilation may cause hypoxemia, hypocarbia, increased alveolar-arterial oxygen difference and an increased ratio of dead space volume to tidal volume.

Therefore, even when an asthmatic patient is asymptomatic by clinical criteria, significant pulmonary dysfunction often exists. It is this knowledge that necessitates close supervision and periodic monitoring by pulmonary function testing in patients with asthma. LOUIS MARCHIOLI, MD
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Emergency Room Treatment of Asthma in Children

PERHAPS the most common type of respiratory emergency encountered in a hospital emergency room is acute asthma. Usually the physician encounters in such a situation a patient in whom the diagnosis has already been determined and then is faced with the task of quickly assessing the asthmatic's clinical status, both by history and physical examination. The initial evaluation should include in the history the duration of the attack, possible precipitating factors (especially infection), and the medications administered before the emergency room visit including dosage and time. It is of special importance to determine whether or not a pressurized adrenergic bronchodilator has been used before administering epinephrine. If gastrointestinal symptoms, particularly hematemesis, are present, aminophylline intoxication or steroid stress should be suspected. The physical examination should include an assessment of the use of accessory muscles of respiration, respiratory effort, presence of pulsus paradoxus, quality and symmetry of breath sounds, and any evidence of infection. An x-ray study of the chest and studies of blood gases can be a part of emergency room evaluation as well. The blood gas findings may indicate hypoxia of a degree not discernible by clinical examination alone.

A numerical "pulmonary index," as described by Bierman and Pierson, is useful to follow the patient's clinical course. A measurement of the expiratory flow rate, such as that obtained with a flow meter, can help a physician evaluate the status of an older child's airway and quickly may indicate severity of a degree which will require intensive therapy and admission to hospital. For example, a peak expiratory flow rate of 80 to 100 liters per minute or less (in an adult) with no improvement in the rate has been shown to correlate with deaths in asthma, as described by Williams.

Once this rapid but thorough assessment of the patient has been made there should be no delay in instituting the appropriate therapy—administration of epinephrine in uncomplicated acute asthma. In children, one to two doses at 20 minute intervals of aqueous epinephrine (1:1,000) 0.01 ml per kg of body weight per dose to a maximum of 0.5 ml may be administered subcutaneously. If there is a satisfactory response, epinephrine (Sus-phrine®) 1:200 then may be administered in a dose of 0.005 ml per kg up to 0.15 ml. Failure to respond to two or three subcutaneous doses of aqueous epinephrine indicates potential status asthmaticus and the need for further treatment in hospital.

In some emergency rooms, additional therapeutic measures including oxygen, hydration, intravenously given aminophylline, aerosolized bronchodilators and steroids are used before admission to hospital. Although controversial, intermittent positive pressure breathing may be used as a method of delivery of aerosolized bronchodilators in the management of acute asthma.

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Intranasal Corticosteroid Sprays

THERE ARE TIMES when the usual measures for control of allergic rhinitis fail. These measures include antihistamine therapy, environmental control and immunotherapy. Formerly, topical application of available corticosteroid preparations was of little benefit; however, in recent years, the use of dexamethasone nasal spray (Decadron® phosphate Turbinaire®) has been introduced. This preparation will give relief to some patients and nasal polyps may be reduced. It may be of particular use in helping to wean a patient from the chronic use of nose drops and sprays. At times, it must be discontinued because of an irritating burning sensation.

Dexamethasone usually is initiated with two sprays into each nostril three or four times per day—the dose should be decreased gradually until the lowest number of sprays that gives reasonable control of symptoms is reached. There will be some absorption of this preparation in doses of 0.5 mg per day or more resulting in the usual side effects of systemic corticosteroids beyond 14 days of use. Nasal septal perforation has been reported in a few cases with long-term use.

A newer preparation, beclomethasone diproprionate (Beconase®), has been used with success

in Europe. This topical corticosteroid is absorbed only partially, giving it a significant advantage over Decadron® in regard to adrenal suppression and systemic side effects at the recommended dosage. Beclomethasone is not presently available for nasal use in the United States, but is available for treatment of asthma (Vanceril®). Other poorly absorbed topical corticosteroids (flunisolide, betamethasone-17, valerate, triamcinolone) are being studied and are expected to be available in the future.

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Inpatient Corticosteroid Therapy for Asthma

SYSTEMIC CORTICOSTEROIDS have a well recognized place in the treatment of patients with asthma in hospital. However, due to adverse side effects their judicious use is warranted. In addition to hydration and correction of blood gas abnormalities and acid-base imbalance, theophylline and sympathomimetics are the primary drugs used in the management of bronchial asthma in hospital. Corticosteroid therapy is indicated in patients who in spite of receiving adequate doses of theophylline intravenously are not responding clinically; in patients receiving long-term oral-aerosol steroids at the time of admission or within 12 to 18 months before admission to hospital, and in patients with asthma receiving long-term oral-aerosol steroids who are admitted for surgical operation or treatment of infection, injury or any other stress.

The rationale behind steroid use is the anti-inflammatory action by which steroids maintain the integrity of the microcirculation and of the cell membrane and stabilize lysosomes. However, these effects may not be relevant to their mode of action in status asthmaticus.

The choice of synthetic steroid is based on its duration of action, which in turn determines the degree of suppression of the hypothalamic-pituitary-adrenal axis. Hydrocortisone or methylprednisolone are preferred, due to their short duration of action. In order to achieve an optimal response, steroids should be given intravenously in doses which exceed the basic secretory rate as determined by plasma cortisol levels. Peak pulmonary function changes after one dose of intravenously given hydrocortisone are seen in 5 hours and decline in 12 hours. Therefore beneficial effects are not expected clinically until 5 to 8 hours from the time of administration. Maximal changes in blood gases are observed when plasma 11-hydroxycorticosteroid levels of 100 to 150 μg per ml are reached. This is achieved by a 5 to 6 mg dose of intravenously given hydrocortisone per kg of body weight.

In practice, Bierman and associates recommend intravenous hydrocortisone at the dose of 7 mg per kg of body weight initially followed by 7 mg per kg every 24 hours, in divided doses. Equivalent doses of intravenously given methylprednisolone could be used instead. If steroids are used for a brief time (three to five days), they can be stopped abruptly. However, longer use often necessitates gradual withdrawal.

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Bronchial Provocation Tests in Patients With Asthma or Hay Fever

IT HAS BEEN KNOWN for some time that the lungs of patients with asthma during a symptom free period will respond to a bronchoconstricting drug, such as methacholine, in doses which fail to cause constriction in nonasthmatic persons. Recent investigation has shown that patients with hay fever who have never had asthma also respond by bronchoconstriction to inhalation challenges with doses of methacholine too small to affect normal subjects. The site of bronchoconstriction, however, differs in the two types of allergy. Whereas both patients with hay fever and those with asthma show a greater sensitivity to the drug in the large central portions of the airway (trachea and bronchi) than normal subjects, patients with asthma appear to have more sensitive peripheral airways than either those with hay fever or normal subjects.

Hay fever may be a serious disorder in its own

right. In some cases it progresses to asthma as well. The inhalation challenge tests described reveal one factor linking the two disorders together.

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Anaphylaxis From Foods

IMMEDIATE SYSTEMIC ANAPHYLACTIC reactions to foods are caused by IgE-mediated hypersensitivity to a food allergen. Such reactions are serious, even life-threatening, and are not rare. The reaction occurs each time the food is eaten, even if the quantity ingested is minute. In some patients, handling the food or inhaling fumes while cooking may trigger an attack. In a patient with anaphylactic food sensitivity, there may be no other manisfestations of allergy, although the coexistence of an atopic history is common. Nuts, eggs, legumes, seafoods and berries are among the more common offenders, but any food is potentially capable of inducing sensitivity. Fortunately most patients with this disease report difficulty with only a single food or a group of related and allergenically cross-reacting foods, such as legumes.

The diagnosis is made in most cases by history. Because of the rapid onset of symptoms after ingestion of the food, the cause of the reaction is obvious to the patient. Sometimes, however, the association with meals is clear, but identification of the specific offending food is in doubt. In these cases skin testing for immediate wheal and flare responses to the suspected foods is appropriate. Because of the risk of a systemic reaction to the skin test, scratch or prick testing should be done first, and only if negative should this be followed by intradermal testing. The skin test is almost always positive, provided that the testing material is fresh. In some circumstances the physician may elect not to test because of fear of reaction to the test or for other reasons. A radioallergosorbent test (RAST) using the suspected food allergen then would be appropriate, since anaphylaxis to foods generally is associated with significant circulating IgE antibodies. The test is almost always positive in cases of anaphylaxis, bronchospasm or angioedema following ingestion of the food.

Occasionally an apparent reaction to a food is caused by a nonfood allergen. Additives, such as preservatives and coloring agents, are potentially allergenic. Penicillin present in milk and milk products has been responsible for systemic reactions in a few patients highly sensitive to the drug.

Specific diagnosis is mandatory for a patient who presents with a history of anaphylaxis after ingesting food, so that the patient can avoid future reactions. There is no evidence at present that oral or parenteral desensitization is effective.

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Human Breast Milk as a Protective Biological Fluid

HUMAN BREAST MILK is an ideal source of nutrition for infants. Although it has been known for some time that babies fed breast milk for the first 9 to 12 months have significantly less morbidity and mortality than infants fed cow's milk, characterization of host defense mechanisms passively imparted to immature infants has only recently been accomplished. Nonimmunological substances found in breast milk include a growth factor for actobacillus bifidus, which lowers the gut pH to decrease the survival of pathogenic organisms; lysozymes; lactoperoxidase, and lactoferritin—all of which destroy and inhibit bacterial growth. The major immunoglobulin in breast milk is secretory IgA which is critical for inhibition of macromolecule (foods and microbe) absorption in the gut. Specific antibody activity against Gram-positive and Gram-negative bacteria as well as viruses has been shown. Both IgG and IgE antibodies are not prominent in breast milk. Several complement components, particularly C3 and C4, also are found. Macrophages make up 90 percent of the cells found in breast milk, while lymphocytes constitute 10 percent of the cells. Both IgA secreting bone marrow derived B lymphocytes and functional thymus derived T cells are present. The protective role of the cellular elements in breast milk has not been elucidated, but is being actively studied.

Finally, human breast milk proteins do not appear to be allergenic to infants in contrast to the potentially allergenic bovine proteins found in

cow's milk. An infant is susceptible to absorption of macromolecules (both microbes and food antigens) in the first year of life. Breast milk may provide this immature host with passive protection at this critical period, as well as with an excellent hypoallergenic source of nutrition.

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Mucocutaneous Lymph Node Syndrome

MUCOCUTANEOUS LYMPH NODE SYNDROME (MLNS) is a recently recognized disease of unknown etiology which has a mortality of 1 to 2 percent. It has occurred with increasing frequency in Japan and is now being recognized in many countries throughout the world, including the United States. It is characterized by fever which persists for more than five days; an erythematous skin eruption; conjunctival congestion; dry fissured red lips; red tongue, palms, and soles; nonpurulent lymphadenopathy; diarrhea; arthralgia and aseptic meningitis. Additional striking features which occur less frequently include carditis; pericarditis; aneurysmal dilatation and thrombosis of coronary arteries; and sudden death. Fatal cases have features which are indistinguishable from infantile polyarteritis nodosa. In some surviving infants there is the transient appearance of coronary aneurysms which subsequently disappear. A few patients have recurrent disease but the vast majority appear to recover completely. Many cases mimic the Stevens-Johnson syndrome. MLNS may actually represent a subdivision of the Stevens-Johnson syndrome as well as one subdivision of infantile polyarteritis nodosa. It has many features of an infectious process and the possibility that the etiologic agent may be viral or rickettsial is currently under investigation in a number of laboratories.

During a collaborative investigation of Japanese children with the syndrome in association with Dr. Kusakawa it was found that early in the course of MLNS there is a 3- to 4-fold elevation of serum IgE level which peaks at 7 to 12 days after onset of the disease and declines over the ensuing 30 to 60 days. This suggests an element of hypersensitivity in the disease, and the vasculitis which commonly occurs suggests a similarity to serum sickness. There is also a significant elevation of total serum IgM but the peak is smaller and later than that of IgE. It is the first nonparasitic acute febrile disease which has been shown to be regularly accompanied by an elevation of serum IgE level and it is the first disease in which a marked IgE response has been shown to precede a significant IgM response. It appears that in patients who have recurrence of the disease the IgE level becomes elevated again, and in patients who have persistent active coronary arteritis IgE levels remain high. Serial IgE levels, therefore, may prove of diagnostic value and help in recognizing continued disease activity.

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The Hazard of IgE Mediated Allergic Reaction After Blood Transfusion

RECENT REPORTS have confirmed the potential risk to infants of passively transferred IgE following exchange transfusion. A single unit of blood or plasma containing a high titer of IgE or an exchange transfusion with blood containing normal amounts of IgE results in a 70 percent uptake by basophils and mast cells throughout the body within 24 hours. By 48 hours maximal fixation has occurred. The skin fixed IgE is shown to persist in significant quantities for at least 31 days. Consequently, the IgE infused in conjunction with a transfusion can place an infant at risk of an anaphylactic reaction for at least one month.

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Immunologic Aspects of Atopic Dermatitis

THE IMMUNOLOGIC CHARACTERISTICS of atopic dermatitis continue to present intriguing questions. Of all the atopic disorders, atopic dermatitis (AD) is most consistently associated with high IgE levels, which appear to be correlated with the extent of skin involvement. In addition, in such patients IgE antibodies to a large variety of food and inhalant allergens are shown by skin test and radioallergosorbent test (RAST). A more in-depth immunological evaluation has shown a normal IgM and IgG response to antigen stimulation, but impaired cell-mediated immunity (CMI), particularly in those patients with severe AD. Clinical evidence for defective CMI includes a tendency to generalized viral infections upon vaccination (vaccinia), recurrent herpes simplex infections, decreased sensitivity to topically applied drugs, and rhus oleoresins (such as poison oak) associated with decreased rhus contact dermatitis, and persistent Trichophyton rubrum infections. *In vivo* testing for CMI has shown decreased sensitization to dinitrochlorobenzene, an agent that causes skin sensitization in more than 90 percent of normal adults, and a decreased incidence of positive delayed hypersensitivity skin tests to several microbial antigens. Recently, *in vitro* testing has shown a striking decrease in peripheral blood thymic-derived T lymphocytes as evidenced by decreased E rosette formation and also decreased mitogen stimulation. In addition, evidence has been presented to show abnormal monocyte chemotactic activity that could contribute to the defective CMI response observed.

An attractive hypothesis relating the defective CMI state to the increase in serum IgE involves the concept of T cell regulation of the IgE response. IgE synthesis appears to be highly T cell dependent. T lymphocytes, by functioning as helper or suppressor T cells, could affect serum IgE levels. The high IgE levels found in several T cell deficient states such as Hodgkin disease and the Wiskott-Aldrich syndrome have been postulated to be on the basis of decreased T cell suppressor function. It has been suggested that a similar mechanism might explain the elevated serum IgE levels in atopic dermatitis.

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EDITORIALS

Perspective on Primary Care

TWO VERY DIFFERENT ARTICLES in this issue address the subject of family practice and primary care. One is more conceptual and distinguishes among family practice, family medicine and family health care. The other is more pragmatic and tells how a community hospital can establish a family practice residency with a firm root in a university center. Both deal with training physicians in a new specialty to provide a new kind of service in something called primary care. But there is as yet no clear agreement about just what is involved in family practice, family medicine, family health care or primary care for that matter. An effort, though perhaps a feeble one, to put things in perspective seems in order.

In the nostalgic days of the horse and buggy doctors in primarily rural America, medical care indeed focused upon the family and upon the caring function. There was then relatively little of scientific worth in the doctor's head or in his bag. As medical science advanced in the 1920's, 1930's and especially in the 1940's and 1950's, attention turned to curing, and most physicians became specialists or subspecialists; this has continued. There was less attention to the whole patient, or to fulfilling most of the needs for care at one stop, so to speak. General practice began to dwindle in both prestige and numbers. In the 1960's the family practice "movement" began. The illusion spread that specialists do not take care of families or of the whole patient, though many did and still do. The formal transformation of general practice into the new specialty of family practice was accomplished. Political pressures developed to train doctors to do primary care, and family practice has ridden the crest of this wave for a decade. And in the last few years the movement has had a strong assist from today's more socially conscious medical students who have sought in large numbers to enter family practice and to provide primary care.

Though neither term is presently well defined, family practice does not seem to equate with primary care. Both terms tend to mean whatever a proponent thinks they should mean. To some, primary care means the first stop at entry into the health care system. Others believe it means care of the majority of ills the flesh is heir to with referral to specialists as necessary. Yet others see it primarily as the prevention of illness and promotion of health, with some aspects of what is coming to be called holistic medicine. And there are also some who do equate primary care with family practice. The proponents of family practice have had some difficulty with the word "family," since a substantial amount of the primary care they believe they should do as family physicians really does not significantly involve the patient's family, and there are a significant number of patients whose family ties are nebulous to say the least. It has been suggested that family be redefined as any group with a past and a future, in an effort to deal with this problem.

The articles in this issue both address training for family practice physicians. Gerber and Massad point out that two distinct kinds of primary care physicians are now being trained. One is chiefly university-based in the traditional disciplines of internal medicine and pediatrics but with substantial emphasis on primary care in the ambulatory care setting, while the other is chiefly community hospital-based for training with more emphasis on the special character of family medicine, which they describe as:

> a theoretical perspective and a body of knowledge with potential application to any medical practice. It places the patient in the context of his environment, puts the medical intervention into a broader perspective, and expands the diagnostic and therapeutic possibilities of the physician to include the impact of the family on the disease process and the impact of the therapy on the patient's support system.

They also emphasize that this approach is as valid for a surgical subspecialist as it is for a primary care physician. Werblun and Martin describe the development of a family practice residency program which seeks to gain some of the advantages of training in both the university and community hospital settings and thereby try to have the best of both worlds.

There are many unanswered questions in this burgeoning field of primary care, which embraces much that is new and much that remains the same. There is obviously much experimentation going on everywhere. The reemergence of a formal focus on caring for the whole patient can only be good,

as is the renewed emphasis on one stop care for many common, uncomplicated, everyday patient care problems. There are dangers that some physicians trained to do only primary care will be tempted to go beyond what should be their limits, and there are dangers that family practice itself will become so enamored of family medicine that the essential grounding in traditional disciplines may be too greatly weakened to the detriment of quality in the care of sick patients. Very recently a major study by the Institute of Medicine of the National Academy of Sciences reminded us that it is the services and not the specialty that should form any definition of primary care, and spelled out the attributes that are essential to the practice of good primary care. This may help to develop a framework for discussing some of these problems and for answering some of the questions that need to be answered.

—MSMW

Hemoptysis 1977

DR. H. LYONS aptly stated recently, "The causes of hemoptysis vary in incidence from series to series and a number of factors influence the frequency in a particular report."[1] In this issue of the WESTERN JOURNAL, Drs. Wolfe and Simmons have expertly reviewed the causes and the factors related to hemoptysis. They also have discussed the management of hemoptysis, in particular the somewhat controversial topic of management of massive hemoptysis. In so doing they have compiled an excellent reference list 62 articles long. Their five tables actually serve as a fine outline for a clear and succinct approach to the problem.

In the 1970's several evolving trends concerning hemoptysis must be stressed, however. Certainly the true incidence of massive hemoptysis (arbitrarily defined as a rate of expectorated blood in ml per 24 hours—most authors use a minimum of 200 ml per 24 hours to define massive) has decreased. The better control of major lung infections causing massive hemoptysis (such as tuberculosis, active and arrested; bronchiectasis; lung abscesses, and necrotizing pneumonia) is the obvious explanation for this fortunate improvement. Specifically, at a busy city-county hospital of 350 beds and a large tuberculosis clinic, I cannot remember a single death due to massive hemoptysis from the aforementioned causes during the 6½ years I have been chief of the medical pulmonary services. This I must admit is probably an unusual, if not an atypical, experience, but still reflects the trends of the 1970's. During this same period we have worked closely with the thoracic surgery service and together have seen approximately two cases per year of massive hemoptysis requiring emergent aggressive thoracotomy and pulmonary resection. During this period I have also seen approximately four to five cases per year of frank hemoptysis (more than "streaking" but less than massive) in patients with a history of previously active tuberculosis. Unless the patients with this past history of tuberculosis and now current hemoptysis have some new active process (such as (1) reactivation of their tuberculosis—very rare, (2) actively infected cysts or residual cavities both by bacterial and aspergillosis—common, or (3) carcinoma—occasional), the hemoptysis was always of short duration and benign. This latter experience of hemoptysis in patients with arrested tuberculosis concurs strikingly with a larger published series by Stinghe.[2] He showed such patients' bleeding is from residual tuberculous bronchiectasis and also uniformly has a self-limited benign course.

The incidence of the two lung diseases, bronchitis and bronchial carcinoma, which usually cause nonmassive hemoptysis is increasing. In regard to this latter group of patients with nonmassive hemoptysis, the primary physician is often faced with the decision of recommending bronchoscopy or not. Since chronic bronchitis and bronchial carcinoma often coexist in the same population, there is no easy or single correct answer to this question. I strongly concur with Drs. Wolfe and Simmons' statement: "In many cases of nonmassive hemoptysis, the cause is obvious and bronchoscopy is not necessary." Several clinical guidelines are helpful, however, in this group where the hemoptysis is usually "streaking of sputum." If the patient is less than 35 years old or is a nonsmoker, the likelihood of primary bronchial cancer is rare. In addition, in the great majority of bronchitic patients findings on radiographs of the chest are normal (excluding hyperinflation and mild increased markings), while in most patients with bronchial cancer with hemoptysis there are abnormal findings on films (mass, infiltrate, atelectasis and the like). Also it is important to remember that blood streaking of sputum secondarily to an acute bronchitis or an exacerbation of chronic bronchitis usually lasts only a day or two, while persistence or recurrence of such blood-streaked sputum or cough is much

more ominous and will require early bronchoscopy.

Putting the use of the 1970's instrument, the bronchofiberscope, into perspective in regard to hemoptysis is necessary. Most 1970's articles on hemoptysis dwell on the use of this fine instrument. In my opinion no bronchoscopy, especially for blood streaking and frank but nonmassive hemoptysis, is complete or adequate without the use of the bronchofiberscope. The diagnostic yield will be improved and the risks are acceptable if the examination is done as soon as possible after the beginning of the hemoptysis requiring bronchoscopy. None the less, this instrument does not replace good clinical judgment and is probably overused for many reasons including monetary considerations. In cases of massive hemoptysis the use of a rigid bronchoscope for emergency examination seems more advantageous than using a bronchofiberscope. The selection of which scope to use for hemoptysis seems less important, however, than the close active communication and cooperation between the experienced pulmonary physician and the skilled thoracic surgeon.

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We Have Come a Long Way

THE HISTORICAL PIECE by Ilza Veith which appears elsewhere in this issue serves as a good reminder of how far medicine in the West, and indeed in the Western world, has come in the last 100 years. In one sense 100 years seems a long time, but compared with today's human life expectancy of more than 70 years, it really is not. It is safe to say that change in medicine has been at least as dramatic as change in the little town of Tiburon, California, since the 1870's, and it could even be that there has been relatively more "progress" in medicine—a statement that today's real estate entrepreneurs in that part of California might conceivably wish to challenge. We have surely come a long way in a mere century and the mind boggles at what medicine will be able to do 100 years hence in the 2070's. Tiburon will seem to have hardly progressed at all by comparison. And it is sobering to realize that some who are being born today will live to see and experience these changes which are inevitable but yet to come. —MSMW

Acute Renal Failure

ACUTE RENAL FAILURE, discussed by Dr. Mendoza elsewhere in this issue, has changed over the last decade.[1,2] The causes are more readily ascertained; the treatment has attained the status of conventional, and the prospects for those children who sustain irreversible damage are better. The decline in the prevalence of poststreptococcal glomerulonephritis has been very noticeable in the Northern and Western United States where scarlet fever and streptococcal pharyngitis were the common infections antecedent to the nephritis. In Hawaii and the southeastern part of the United States where the climate is warm and humid, the disease is prevalent and its antecedent infection is impetigo.[3] The seasonal incidence and immunologic responses differ depending on whether pharyngitis or skin infection is the antecedent. In other respects the disease is the same. Better housing and nutrition, more effective use of antibiotics or the natural history of the disease may account for the decline in streptococcal pharyngitis and the associated decrease in nephritis induced in this way. The good prognosis customarily associated with nephritis affecting children appears to continue.[4,5]

The hemolytic-uremic syndrome, described in detail by Dr. Mendoza, is enigmatic. It appears to be a modern disease not present to any degree two or three decades ago. It is more prevalent in Argentina, South Africa and the Western United States. Its cause remains obscure. Our experience has been that the disease may leave the kidney severely injured more often than the experiences cited by Dr. Mendoza.[6] The children who suffer permanent damage are among those who are severely oliguric or anuric on admission. However prolonged, oliguria, even to six weeks, is compatible with complete recovery.

Acute tubular necrosis as noted often is preventable. The tendency, common a decade ago, to have children referred who had been given excessive quantities of 5 percent glucose and 0.2 percent saline solution (the ward all-purpose solution) to the point where they had hyponatremia, has fortunately reversed.

Giving isotonic sodium chloride, Ringers lac-

tate solution or chloride bicarbonate solutions to children whenever their perfusion is compromised is very important. Where acidosis coexists, as it often does, we use an ampule of 50 ml (50 mEq) of sodium bicarbonate added to 1 liter of 0.45 percent of sodium chloride (this solution has the following composition in mEq per liter: sodium, 121; chloride, 73; bicarbonate, 48) and infuse the solution at a rate of 20 ml per kg of body weight per hour until it is clear that perfusion is adequate. At that point, further expansion of extracellular fluid volume is contraindicated. Children with the nephrotic syndrome are prone to the development of acute tubular necrosis (ATN). When they have been in remission and suddenly have a relapse with massive proteinuria and contraction of plasma volume, shock and ATN may develop.[7] They may need a prompt infusion of extracellular-like fluid to create enough edema to support circulation. If acute tubular necrosis does occur, it usually is not severe.

We have found it useful to give mannitol to children with acute hemoglobinuria or myoglobinuria. We give 0.5 grams per kg of body weight as a 20 percent solution over a 15 to 30 minute period and then match further fluid input to urine output (or give slightly less fluid than urine output) using a 4 percent mannitol solution in 0.2 percent sodium chloride until the urine is seen to be free of pigment.[8] Where there has been an acute release of myoglobin or hemoglobin the clearing usually takes less than 12 hours. This method avoids significant changes in extracellular fluid volume or osmolality.

Acute renal failure in the neonatal period is a special case that has been the subject of a recent review.[9] Therapy of acute renal failure has been well defined. The challenge of manipulating body composition that made treatment exciting to physicians and sometimes put a patient at risk has given way to straightforward strategies so clearly outlined in Dr. Mendoza's review. I would only emphasize one point and suggest another. Undertaking hemodialysis or peritoneal dialysis by an experienced group at a relatively early stage on well defined criteria, uncluttered by attempts to avoid dialysis, has made an important difference. Hypertonic dialysate (4.5 percent dextrose solution) used as peritoneal dialysate is very helpful in removing extra fluid. Adequate dwell times (longer than 30 minutes) are needed to avoid inducing hypernatremia and to assure effective removal of extra fluid. While dialysis even in experienced hands carries some risk, the risk is minimal compared with leaving a patient with serious volume or compositional problems which dialysis could readily correct.

The point I would draw attention to is the probable advantage of more aggressive nutritional therapy. There are data in adults that suggest the value to patients of giving intravenous nutrition that provides 50 to 100 percent of needed energy and amino acids.[10,11] In children with renal failure, net urea nitrogen production was progressively suppressed in response to increases in glucose administration given through a catheter placed in a central vein. Net urea nitrogen production was further reduced and nitrogen retained as body protein when these children were also given essential amino acids.[12] The risk of central vein catheters while appreciable probably is less than the risk of severe malnutrition. While no clear guidelines for instituting its use have emerged, experience with intravenous nutrition in surgical patients strongly supports the initiation of intravenous nutrition in patients with renal failure before cachexia has become obvious. Since children have a disadvantage in that the ratio of energy expenditure to energy stores is less,[13] it would seem logical to begin therapy soon after the onset of an illness in which intake is compromised. Undernutrition may be another factor, and a preventable one, that makes children with renal failure more susceptible to infection.[14]

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CASE REPORTS

Refer to: Garner JT, Jacques S: Positional vertigo and bruit—A surgical emergency. West J Med 127: 414-416, Nov 1977

Positional Vertigo and Bruit —A Surgical Emergency

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ATHEROMATOUS DISEASE of the extracranial arteries as a major cause of stroke has been amply documented.[1-11] Furthermore, it is now apparent that transient ischemic attacks (TIA) can be a prelude to stroke and signify serious underlying vascular disease.[1] Retrospective analysis indicates that many cases of cerebral infarction are heralded by single or multiple episodes of transient cerebral ischemia.[2] We present three cases in which vertigo produced by positional change of the head was superimposed on a TIA symptom complex. Each of these patients had a high-grade stenosis of the internal carotid artery without evidence of pathology in the vertebral circulation. The symptoms were eliminated by carotid endarterectomy.

Reports of Cases

CASE 1. A 61-year-old white man was seen because of intermittent symptoms of visual disturbance and one episode of transient aphasia over several weeks. A bruit was auscultated over the left carotid bifurcation in the neck. Arrangements were made for admission to hospital and angiography. Two days before admission, the patient reported vertigo when he turned his head. These spells could be brought on at will by looking to the right. The patient was admitted to hospital and four-vessel angiography was carried out which showed a 90 percent stenosis of the left internal carotid artery (Figure 1). The remainder of the examination gave essentially negative findings. Plans were made for carotid endarterectomy the following day. During the night a massive cerebrovascular accident occurred, leaving the patient with a persistent hemiparesis and nominal

Figure 1.—Pronounced narrowing at carotid bifurcation is shown (case 1).

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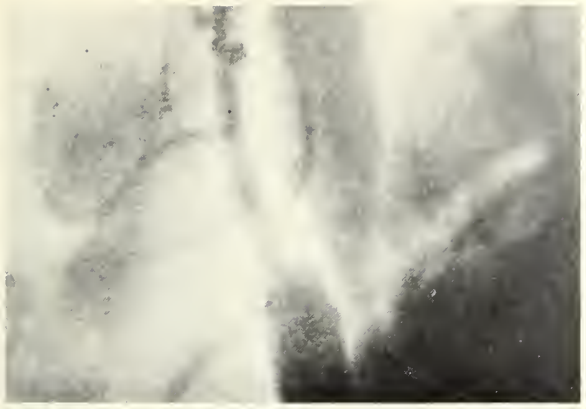

Figure 2.—String-like segment of internal carotid is evident (case 2).

aphasia. Subsequent angiography showed an occluded internal carotid artery.

CASE 2. A 55-year-old white man was seen because of intermittent attacks of left-sided weakness and numbness of six months' duration. Three days before admission he noted the onset of vertigo on turning his head. Examination showed a loud bruit over the right carotid bifurcation. On the morning of consultation the patient stated that the episodes of vertigo on head turning had increased in intensity. Based on the experience in case 1, immediate four-vessel angiography was carried out which showed a 90 percent stenosis of the right internal carotid artery by a large arteriosclerotic plaque (Figure 2). The vertebrobasilar circulation was normal. The patient was taken immediately to surgery from radiology and a successful endarterectomy was done with complete resolution of symptoms.

CASE 3. A 57-year-old white man, a physician, was seen with a history of fleeting attacks of aphasia and lapses of attention. He had not planned to seek medical attention until after the Christmas holidays but became concerned at the onset of vertiginous attacks of mounting severity on head turning or extension. A loud bruit was auscultated over the left carotid bifurcation. Immediate four-vessel angiography showed a 90 percent stenosis of the internal carotid artery on the left (Figure 3), a 40 percent stenosis on the right and a normal vertebrobasilar circulation. Prompt endarterectomy was followed by complete amelioration of symptoms.

Findings on vertebral angiograms in all three cases were normal.

Figure 3.—Pronounced narrowing of internal carotid artery is shown, with imprint of large plaque and superimposed clot projecting into lumen from anterior portion of vessel wall (case 3).

Discussion

Transient ischemic attacks are episodes of reversible focal neurological dysfunction caused by an interruption of blood supply to an area of the brain. The interruption is usually vascular in origin but may also have a cardiac-related cause or a combination of both. Embolization of fragments of vessel wall or atheroma and hemodynamic changes are the usual mechanisms invoked to explain TIA's.[3-6] The importance of TIA's as harbingers of impending stroke is becoming increasingly more apparent.[1,2,7] It therefore appears that surgical correction of atheromatous lesions, especially of the carotid bifurcation in selected patients, is a major therapeutic approach to prevent catastrophic neurological dysfunction.[6,9]

Classically, the manifestations of TIA's are classified according to the site of focal cerebral ischemia with vertigo being ascribed to the vertebrobasilar system.[2,6,10] The cases presented here would suggest that vertigo, accentuated by a change in head position, can be a sequela of high-grade stenosis of the internal carotid artery in the neck. The three patients shared a common symptom complex of occasional TIA's, sudden onset of positional vertigo, bruit over the carotid bifurcation and a 90 percent stenosis of the affected carotid artery. In no case was there a pathologic condition evident in the vertebrobasilar circulation. The pathogenesis of the positional

vertigo is probably due to kinking and occlusion of the stenotic portion of the internal carotid artery when the head is turned. The frightening nature of the symptom immediately caused each patient to resume a neutral head position. In the first patient, total occlusion probably occurred because of absence of response to the symptoms during sleep. In each of the operated cases there was complete immediate resolution of symptoms.

It is of interest that a recently published self-evaluation of stroke gave remarkably similar symptoms to those in our cases, as well as similar angiographic findings.[11] The "dizziness" in this instance was ascribed to a lesion of the posterior internal capsule based on recent neurophysiological data.[12,13]

The authors conclude that the symptom complex described here may constitute an acute surgical emergency and should be treated as such.

Summary

Three cases of atheromatous disease of the carotid artery heralded by vertigo on head turning are described. In all cases auscultation showed a bruit and angiographic findings were consistent with pronounced carotid stenosis and plaque formation without involvement of the vertebral circulation. The authors stress the need for immediate evaluation in patients with this symptom complex.

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Refer to: Liebman WM, Rosental E: Benign lymphoid hyperplasia of the colon. West J Med 127:416-418, Nov 1977

Benign Lymphoid Hyperplasia of the Colon

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BENIGN LYMPHOID HYPERPLASIA of the colon in children has been frequently confused with multiple polyposis of the colon, resulting in unnecessary surgical procedures.[1] Yet, this disease has distinctive roentgenographic features suggestive of its diagnosis, although a biopsy is necessary for confirmation of the nature of the nodular lesions.[2,3] This paper describes the case of an infant with benign hyperplasia of the colon and reviews the current state of knowledge about this disease.

Report of a Case

A 10-month-old girl was admitted to the University of California Medical Center with a history of recurrent blood, predominantly occult, in the bowel movements since 6 months of age. Macrocytic megaloblastic anemia was diagnosed after extensive study including urine and plasma amino acid screen (normal), serum folate and vitamin B_{12} levels (low) and bone marrow examination. Treatment was begun with folate and vitamin B_{12}. There was no response to this regimen, and a 1-unit transfusion of whole blood was administered by the private physician, which raised the hemoglobin level from 7.5 grams per 100 ml to 9.0 grams per 100 ml and the hematocrit reading from 23 to 27 percent.

The patient weighed 4.2 kg (9.3 pounds) at birth. The pregnancy had lasted 40 weeks. She fed well initially but subsequently had isolated episodes of vomiting or atypical, segmental rashes while receiving several types of formula and baby

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Figure 1.—Small mucosal nodules are present throughout the colon.

foods—for example, SMA®, Similac ISOMIL® and fruits. She subsequently improved on a regimen of goat's milk. At 2 months of age she had a possible major motor seizure associated with a urinary tract infection but no fever. Findings on an electroencephalogram (EEG) were mildly abnormal but nonspecific in nature. She was treated with sulfisoxazole (Gantrisin®) and phenobarbital. At 6 months of age findings on a repeat EEG were normal, and phenobarbital was discontinued. Throughout, the growth pattern has been within normal limits. At present, the patient's diet consists of Pregestimil®, rice, and applesauce, and 0.6 ml per day of ferrous sulfate (Fer-In-Sol®).

The family history was unrevealing except for a 5-year-old sister with infectious mononucleosis. The social history and review of systems were unremarkable.

On physical examination, height was 70 cm and weight was 8.44 kg (18.6 pounds). There were several drying, pink, maculopapular lesions over the facial area. No other significant physical findings were observed. Laboratory studies gave the following values: hemoglobin, 12.4 grams per 100 ml; leukocyte count, 8,300 per cu mm with a normal differential; serum iron, 77 μg per 100 ml; total iron-binding capacity, 267 μg per 100 ml; serum folate, greater than 20 ng per ml; reticulocyte count, 0.7 percent; platelet count 504,000; hemoglobin electrophoresis with F, less

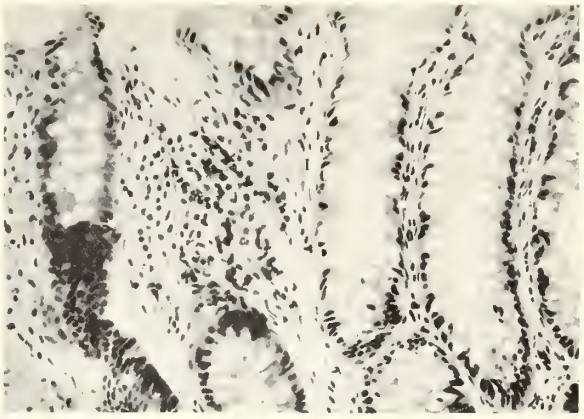

Figure 2.—Rectal biopsy specimen. A collection of mature lymphocytes is present.

than 2 percent and A, 100 percent; and quantitative immunoglobulins (G,M,A,D and E), sweat chloride test, total lymphocyte count and corpus albicans skin test all within normal limits. Findings on an upper gastrointestinal series were unremarkable. An air contrast barium enema showed multiple nodular lesions of the colon (Figure 1). A pertechnetate scan for Meckel diverticulum was negative. Results of upper endoscopy and midduodenal biopsy showed no abnormalities. Sigmoidoscopy showed minimal erythema of the rectum without increased friability, ulceration or polypoid lesions. The rectal biopsy showed the presence of focal collections of lymphocytes without other abnormalities (Figure 2). No treatment was instituted, and the patient has remained asymptomatic during a five-month followup.

Discussion

Lymphoid hyperplasia of the small as well as the large intestine is uncommon in children but has been observed in a number of clinical situations.[2,4] This entity probably represents the normal response of lymphoid tissue to various stimuli.[1] When limited to the small intestine, it has been associated with immunodeficiency (for example, acquired agammaglobulinemia, selective IgA deficiency).[5,6] The association with giardiasis has been noted, as has that with eczematoid dermatitis and pernicious anemia. However, the role of giardiasis has been unresolved since hypogammaglobulinemia has also invariably been present in these cases.[5,6] Lymphoid hyperplasia of the colon has also been associated with the above conditions, as well as with familial adenomatous

polyposis and Gardner syndrome.[7] The general age range is 6 months to 12 years.

The hyperplasia is characterized radiologically by small, relatively uniform, umbilicated polypoid lesions, involving all or part of the large intestine. Unique for lymphoid hyperplasia is the presence of a small amount of barium in the center of the polyps; that is, an umbilication at the apex of the lymphoid nodule.[1] This umbilication has *not* been observed in multiple polyposis or juvenile polyps of the large intestine.[1]

Histologically, the submucosal nodules are composed of lymphoid follicles within the normal mucosal pattern. The follicles consist of mature lymphocytes and reticulum cells with or without germinal centers.[8]

The symptomatology in this condition has included vague abdominal pain, sporadic or recurrent (40 to 80 percent), rectal bleeding (0 to 70 percent), constipation or diarrhea (10 to 40 percent).[1,3,9] The rectal bleeding has been microscopic as well as macroscopic in nature and may be persistent. Anemia is usually not present. There are no specific laboratory studies.

Because of the earlier confusion with multiple polyposis of the colon, treatment has included radiation therapy or colectomy, as well as prolonged corticosteroid administration.[1] When lymphoid hyperplasia has been diagnosed, no specific treatment is indicated since a spontaneous regression usually occurs within months.[1,3] If the rectal bleeding persists or if severe abdominal pain occurs in this condition, treatment with corticosteroids (prednisone) can be instituted for two to four weeks.

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Refer to: Kaplan AM, Itabashi HH, Yoshimori R, et al: Cerebral abscesses complicating neonatal Citrobacter freundii meningitis. West J Med 127:418-422, Nov 1977

Cerebral Abscesses Complicating Neonatal Citrobacter freundii Meningitis

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THE CITROBACTER GENUS of bacteria, although once regarded as nonpathogenic, has been responsible for many well-documented pathologic conditions, especially in compromised hosts. These include urinary tract, pulmonary and bone infections;[1] gastroenteritis;[2] gangrenous ulcer with septicemia,[3] perinephric abscess[4] and meningitis.[5-10] Species of Citrobacter are still a rare cause of meningitis, but several reports have appeared in recent years implicating this group of organisms as the cause of neonatal meningitis with high morbidity and mortality. Development of a cerebral abscess complicating meningitis due to Citrobacter freundii has been reported before but without specific bacterial documentation. In this report, we provide bacteriologic and pathologic confirmation of this uncommon but devastating complication.

Report of a Case

A white infant girl was transferred to Harbor General Hospital at the age of six weeks for evaluation and treatment of intractable Citrobacter freundii meningitis.

The infant was born to a 24-year-old primipara following a normal term pregnancy and delivery. Birth weight was 3.1 kg (6.8 pounds). The

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infant went home on the third day, where she ate poorly and was lethargic; her crying was reported to be weak. On the fifth day, fever and a bulging fontanelle were noted. That evening right-sided clonic seizures occurred and the infant was admitted to the referring hospital.

On admission, temperature was 99.6°F (37.6°C), respirations 40 per minute, and a pulse rate of 140 beats per minute. Head circumference was 33.5 cm, and the fontanelle was bulging. There were right-sided clonic seizures with ocular deviation to the right. The neck was supple. Muscle tone was generally increased, but no paralysis was noted. Grasp and Moro reflexes were good.

Initial laboratory findings were as follows: Hemoglobin value was 14.2 grams per 100 ml and leukocyte count was 20,700 per cu mm with 59 percent polymorphonuclear leukocytes (PMN), 16 percent lymphocytes, 20 percent monocytes, 4 percent myelocytes and 1 percent eosinophils. Lumbar puncture showed grossly turbid cerebrospinal fluid (CSF). CSF cell count was 17 red cells per cu mm and 1,490 leukocytes per cu mm of which 88 percent were PMN. CSF glucose was 40 mg per 100 ml and total protein was 838 mg per 100 ml. No organisms were seen on stained smear.

The infant was immediately started on a regimen of ampicillin, 200 mg per kg of body weight per day given intravenously, and kanamycin, 15 mg per kg per day given intramuscularly, which led to some clinical improvement but without decrease in the CSF cell count. Citrobacter freundii was cultured from the CSF and was found to be resistant to ampicillin. Therapy was then started with cephalothin, 100 mg per kg of body weight per day given intravenously, again without decrease in the CSF cell count. Over the following three weeks the patient received gentamicin given intravenously and intrathecally, chloramphenicol given intravenously, and a second course of ampicillin, all of which failed to clear the CSF of inflammatory cells.

On transfer to Harbor General Hospital, the infant was irritable and had opisthotonos. The pulse rate was 164 beats per minute, respirations 60 per minute and temperature 102.2°F (39°C). Head circumference was 37.5 cm. The fontanelle was full, and there was nuchal rigidity. Liver was palpable 3 to 4 cm below the right costal margin, but the remainder of the general examination findings were within normal limits. Cranial nerves were intact. There was generalized increase in tone and hyperreflexia. Right-sided decorticate posturing was observed, but a Moro response was symmetrical. Head control, sucking and grasp reflexes were poor.

A lumbar puncture was traumatic, but the CSF glucose value was 24 mg per 100 ml and total protein 266 mg per 100 ml. No organisms were seen on smear, and cultures showed no growth. Serum immunoglobulin levels were as follows: IgA, 32 mg per dl (normal, 4 to 36 mg per 100 ml); IgG, 275 mg per dl (normal 200 to 950 mg per 100 ml); IgM, 125 mg per dl (normal, 20 to 80 mg per 100 ml), and IgD, 0 (normal, 0 to 6 mg per 100 ml). Chest and skull x-rays were normal. An electroencephalogram showed diffuse slowing with epileptogenic foci in the left parietal, left temporal and right parietal regions. A brain scan with Technetium 99m (^{99m}Tc) pertechnitate showed a large "cold" area within an area of increased uptake in the left posterior parietal region consistent with an abscess. Two other smaller areas in the left temporal and right parietal regions were also considered suspicious. Subdural taps were dry. Cerebral angiography showed findings consistent with hydrocephalus but without definite mass effect.

The infant was continued on chloramphenicol therapy, 100 mg per kg of body weight per day given intravenously. Following angiography, frequent seizures were noted which responded poorly to large doses of anticonvulsant medications. In view of the hydrocephalus, an external ventricular shunt with a low pressure Holter valve was placed, but the infant's condition continued to deteriorate. She died at the age of 7½ weeks.

Bacterial Isolation

Three CSF specimens and a ventricular fluid specimen were submitted for culture. Citrobacter freundii was recovered from all specimens using sheep blood and chocolate agar plates for primary isolation. The Gram-negative organism was identified using the differential media, R/B, of General Diagnostics, Inc. Negative reactions recorded were phenylalanine deaminase, indole, lysine decarboxylase, ornithine decarboxylase and raffinose. Positive reactions were hydrogen sulfide production, gas from glucose fermentation, motility, citrate utilization, lactose, rhamnose, sorbitol and arabinose fermentation.

Figure 1.—Coronal section through the posterior parietal lobes showing bilateral abscesses.

Autopsy Findings

General autopsy findings included focal, healed pneumonitis; mild, focal, chronic pancreatitis; acute and chronic passive congestion of the liver, spleen, and adrenal glands; mild, focal, adrenal cortical nodular hyperplasia, and stress ulcers of the stomach.

The brain weighed 470 grams and showed moderate flattening of the gyral surfaces and focal areas of softening of the parietal lobe convexities on both sides. Approximately 25 ml of greenish, purulent material escaped from a cortical defect created through an area of softening in the left parietal lobe. Leptomeninges were cloudy over the convexities and thickened and opaque over the ventral aspect of the brain stem. Sections showed the presence of three separate large abscesses filled with yellowish, purulent exudate—one occupying the frontal white matter, anterolateral to the anterior horn of the left lateral ventricle; a second largely replacing the white matter of the left parieto-occipital lobe with ventromedial displacement of the posterior horn of the lateral ventricle, and a third abscess occupying a similar position as the second but on the right side (Figure 1). Traces of purulent exudate were found throughout the lateral and third ventricles, and the fourth ventricle was nearly filled. The aqueduct of Sylvius was grossly occluded at its midpoint.

Studied microscopically, the abscesses were shown to be chronic with a content of necrotic debris and persistent acute inflammatory cells and a wall of a relatively wide zone of granulation tissue with prominent neovascularization surrounded by an atypically wide zone of astrogliosis (Figure 2). In the latter zone, the astrocytes were rather numerous and hypertrophied. In other areas, the cerebral white matter showed diffuse astrogliosis, especially where white matter faced the ventricles. Rare, small foci of noninflammatory necrosis were noted, some with calcification. Leptomeninges were mildly fibrotic and the spaces contained sparse inflammatory cells. The ependyma of the lateral ventricles was greatly attenuated in areas, and the ventricles contained cellular debris and polymorphonuclear leukocytes. The cerebral cortex was intact for the most part except where the abscess approached the surface.

Figure 2.—Photomicrographs of abscess wall consisting of layers of inflammatory cells, zone of granulation tissue, and a wide zone of astrogliosis extending into surrounding white matter. (H and E × 42)

Comment

The classification of Bacterium freundii has been controversial since it was first isolated in 1928.[11] The organism has been reclassified variously as Citrobacter freundii, Escherichia freundii, Colobactrum freundii and Paracolobactrum freundii.[12] The accepted name today is Citrobacter

freundii, but biochemically closely related microorganisms such as Escherichia intermedium and the Bethesda-Ballerup group have been assimilated into this genus. The genus is therefore heterogeneous, and at least two species exist by current classifications: C. freundii and C. diversus.[13] C. diversus is considered to be heterogenous by some investigators and has been divided into C. koseri and a new genus, Padlewski or Levinea. The eighth edition of *Bergey's Manual of Determinative Bacteriology* speciates Citrobacter into C. freundii and two biotypes (a and b), or C. intermedius which is synonymous with Padlewski or Levinea and C. koseri, respectively.[11]

A review of 13 cases of Citrobacter meningitis from the literature (Table 1) shows the following: 6 of 9 cases were males; 10 of 13 infants were either premature or of low birth weight; 10 of 13 had symptoms before 14 days of age, and, in general, the prognosis conformed to the universally poor statistics for neonatal meningitis with mortality approaching 50 percent and neurologic residua in 40 percent. Cerebral abscesses were reported to have occurred in at least two of the cases but are incomplete in details.

The diagnosis of this disease, as in all neonatal meningitides, was difficult. There is no characteristic clinical constellation of signs and only a high index of suspicion in a premature infant with vague symptoms may establish an early diagnosis. Radioisotope brain scan, as shown in this report, is a valuable tool and may be more sensitive than angiography in confirming the diagnosis of cerebral abscess.[14] The treatment of choice is a combination of prolonged parenteral antibiotic treat-

TABLE 1.—*Review of Cases of Citrobacter Meningitis*

Author(s)	*Age (Days)*	*Sex*	*Gestation/Weight (Week) (Grams)*	*Organism*	*Course*	*Postmortem Findings*
Harris and Cone[5] 1960	49	♀	Term/—	E. freundii*	Seizures, hydrocephalus, psychomotor retardation, and rigidity	..
	2	♂	36/2,250	E. freundii*	Died	Acute leptomeningitis with abscess of the right cerebrum
Shortland-Webb[6] 1968	35	♂	32/1,800	C. freundii	Died	Purulent exudate covered the cerebellum and both cerebral hemispheres
Cavalieri and Piacentini[7] 1968	4	♂	Term/3,500	C. freundii	Aqueductal stenosis with hydrocephalus	..
Gwynn and George[8] 1973	4	♂	33/2,000	C. koseri	Died	Widespread necrosis of right hemisphere with meningeal congestion and base exudate
	6	♀	Twin pregnancy	C. koseri	Superficial brain abscess, subdural empyema, hydrocephalus, and porencephalic cysts	..
	13	♂	Term/1,720	C. koseri	No sequelae	..
	9	♂	32/1,820	C. koseri	Hydrocephalus with extraventricular cystic cavities and subdural empyema	
Gross et al[9] 1973	<7	?	Premature	C. koseri	Died	No postmortem examination done
	<7	?	Premature	C. koseri	Died	No postmortem examination done
	<7	?	Premature	C. koseri	No sequelae	..
	7	?	37/—	C. koseri	No data	..
Tamborlane and Soto[10] 1975	42	♀	38/2,532	C. diversus	Aqueductal stenosis with hydrocephalus	..
Present case	6	♀	Term/3,100	C. freundii	Died	See text for postmortem findings

*Escherichia freundii—former classification of Citrobacter freundii

ment and early surgical management of neurologic complications.

The patient of this report was somewhat unusual in that she was born following a term pregnancy, birth weight and delivery were normal, and there were no predisposing obstetrical complications. There was no evidence of underlying cardiac or other disease, and the infant was immunologically intact. We conclude, as others have, that not all infections due to the Citrobacter group of organisms represent opportunistic infections in a host with compromised resistance, but rather that the Citrobacter group should be regarded as important pathogenetic organisms.

Summary

Bacterial meningitis developed in an infant during the neonatal period. Failure to respond to aggressive antibiotic therapy was shown at postmortem examination to be due to multiple brain abscesses. The causative organism was proved to be Citrobacter freundii.

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Luring the Husband to Participate in Marital Counseling

If a marriage is troubled enough to involve both husband and wife in counseling, then you must lure him in. It's usually the husband who does not want to come in. And if she says, "Well, I know darned well he won't come in," then the trick, which works for almost all cases, is for you to intercede in the following fashion. . . . Call him up and say something like, "I saw your wife yesterday in the office. I think she's got some problems I should talk to you about." . . . And things like, "Well, I'll tell you. I know your wife and she hasn't been quite her smiling happy self lately and I know you'd like to change that. And I think you can help her out. So come in at such-and-such a time and we'll talk it over."

—BEVERLEY T. MEAD, MD, *Omaha*
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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Patient's Access to Physician's Records

TO THE EDITOR: I liked your editorial in the September issue, "Patient's Access to Physician's Records," even though you come out on the opposite side from me.[1] I think you are certainly right about the possibility of patients misinterpreting data and terms, for instance, but I wonder if giving them their records wouldn't result in a more informed public, and one more respectful of their own limitations, in time. I also share your attitude toward third parties, who are likely to respect the rights of neither patient nor doctor.

In general, though, I think we are in a new age, and people will be less and less willing to take things on faith, from a doctor or anyone else. In a lot of ways this is too bad, but I'm afraid that's the way it is. If we as physicians keep things to ourselves, I think the general tide of society will believe less and less that we do it for their benefit. Therefore, I think it is up to us to make the records available, but take steps to ensure that good results do come of it.

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Patients at Risk for Postoperative Pulmonary Embolism

TO THE EDITOR: A method for identifying patients at risk for postoperative pulmonary embolism has been developed at this institution. It requires the correlation of patient body surface area and anesthesia time and proved reliable in both prospective and retrospective studies. This system can be used to identify at-risk patients preoperatively, thus providing a more rational use for preoperative and postoperative scanning as well as for heparin prophylaxis.

Patient body surface area is calculated in square meters and multiplied by anesthesia minutes (as opposed to surgical minutes) to give a surface area—anesthesia minutes value (SAM). By way of example, the SAM value of a patient may be calculated as follows:

Surface Area × Anesthesia Minutes = SAM Value
1.821 m^2 × 120 minutes = 218 SAM

The SAM values and the incidence of pulmonary embolism in a prospective study of 40 abdominal and 30 extra-abdominal cases are shown in Table 1. Note that as the SAM values increase so does the incidence of pulmonary embolism. Patients become at risk for embolism in abdominal procedures at SAM values of 300 or more and at risk in extra-abdominal procedures at SAM values of 400 or more.

TABLE 1.—*SAM Values and Incidence of Pulmonary Embolism for Abdominal and Extra-abdominal Procedures*

Abdominal		*Extra-abdominal*	
SAM Values	*Incidence (Percent)*	*SAM Values*	*Incidence (Percent)*
<200	10	<200	0
200-300	15	200-400	5
300-400	30	>400	12.5
>400	43		

The various studies have reported asymptomatic pulmonary emboli up to 20 percent.[1,2] In the study conducted here, the incidence of asymptomatic pulmonary emboli was 22 percent in the abdominal group and 3 percent in the extra-abdominal group. The relationship between patient size and anesthesia time proved to be reliable in predicting postoperative embolic events. Anesthesia time is important as the very nature of surgical operations produces a state of hypercoagulability and as anesthesia time lengthens, the opportunity increases for activated clotting components to unite. Patient size is more difficult to

explain. This could be mechanical in that the larger the person the larger the vascular and capillary bed and, therefore, the more opportunity for blood flow to become sluggish.

The fact that embolism in abdominal surgical procedures is more frequent and occurs at a lower SAM value may be explained by two factors. One is the result of stasis which is primarily a function of sluggish blood flow permitting fibrin and red cells to form a clot. The other is injury to the vessel endothelium which causes the platelets to become more adhesive and to gather at the injured site thereby forming a nidus for clotting.[3] It is conceivable in abdominal procedures that obtaining adequate exposure by various means would be capable of producing venous injury. Retractors, packing or holding the bowel away from the surgical site, could apply external pressure on major vessels to the point where intimal damage occurs.

Patient position during operation emerged as an important factor as postoperative emboli were absent in patients with SAM values of less than 200 unless the patient was placed in a position on the operating table other than supine or prone. It is well established that stasis is a very important factor and probably explains in a large measure the findings of increased risk of pulmonary embolism in the non-true prone/supine position.

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Recording Informed Consent

TO THE EDITOR: Two recent communications to the WESTERN JOURNAL have expressed negative opinions on the value of obtaining written (as opposed to oral) informed consent.[1,2] Unlike the two authors, I am not an attorney. Perhaps it is for this reason that I find it difficult to understand why this situation should differ from other fields of law, such as contracts, rental agreements, leases, agreements to purchase and the like—in all of which the written form is either preferable or required.

In addition, physicians should be aware that the Food and Drug Administration[3] and the National Institutes of Health require informed consent in writing for all investigational drugs in phase I and phase II studies, and in most instances in phase III studies. Similar requirements are enforced by the human research committees of all hospitals with which I am familiar.

In essence, of course, all consents are "written" unless they are tape-recorded, an option not discussed by the two authors. I fail to see why a potentially self-serving handwritten statement by a physician of what he told a patient is preferable to a typed or printed consent, signed by the patient himself, including the patient's statement that his questions have been answered, and naming the specific risks and benefits of the procedure in question, as required in *Cobbs vs Grant.*

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Phagocytosis in Chronic Myelocytic Leukemia

TO THE EDITOR: With great interest I read the report in the February issue by Shanley and Cline[1] on phagocytosis of hematopoietic cells by blast cells in a patient with chronic myelocytic leukemia (CML) blast crisis.

The authors mention in the discussion that CML is a clonal disease of the pluripotential stem cell. However, they do not consider the possibility of the phagocyting blast cells being immature members of the megakaryocytic compartment. Several data support this suggestion. In the majority of CML an increase of the megakaryocytic cell-line is observed in the bone marrow.[2] Reports on megakaryoblastic proliferation in CML blast crisis have been published.[3-6]

In our own material (unpublished) concerning CML blast crisis we have noted in several patients very suggestive evidence of megakaryoblastic proliferation on pure morphological grounds as well as on histological and cytochemical observations. The two cytochemical markers of the large blast cells in the report (negative in the peroxidase and alpha naphtyl butyrase reactions) make a monocytic origin less likely but do fit very well in the megakaryoblastic concept.

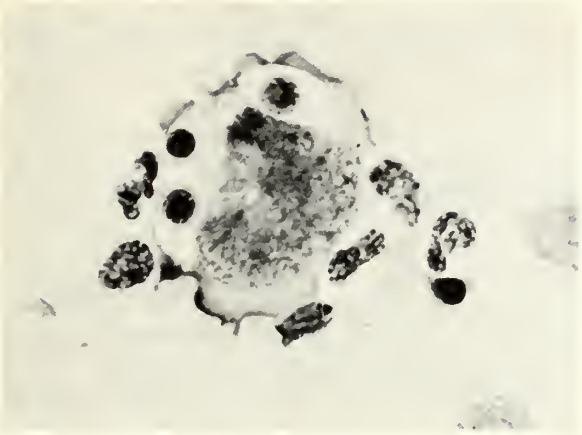

Figure 1.—Megakaryocyte enclosing three erythroblasts.

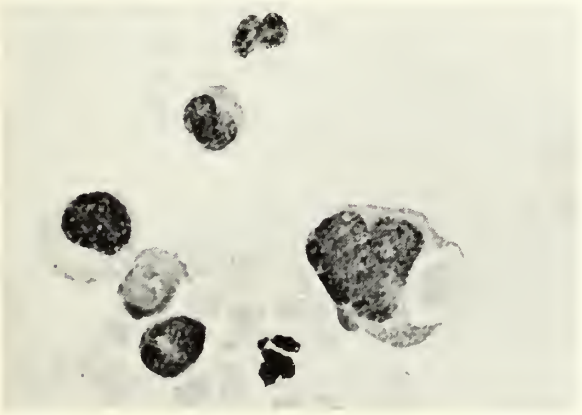

Figure 2.—Blast cell enclosing an erythrocyte.

Li and co-workers[7] observed a specific pattern of megakaryocytic cells in the nonspecific esterase reactions: a completely negative reaction in the alpha naphtyl butyrase reaction with a strong positivity for the alpha naphtyl acetate. This pattern was recently confirmed by Grusovin and Castoldi,[8] and we found the same.

Megakaryoblastic differentiation in Shanley and Cline's case is therefore more acceptable. In that case it is likely we are not dealing with real phagocytosis, but with a form of pseudophagocytosis, so-called emperipolesis. This phenomenon is well known in megakaryocytic cells.[9-11] In emperipolesis a cell is enclosed within the megakaryocyte without being destroyed itself or causing any visible damage to the "host" cell. Characteristic is the halo surrounding the enclosed cell (Figure 1). We did observe emperipolesis in the blast cells of a patient with megakaryoblastic leukemia (see Figure 2).

In conclusion we consider that the "phagocyting" cells in the report of Shanley and Cline are megakaryoblasts, which fulfill both criteria of emperipolesis: a halo surrounding the enclosed cell and no signs of damage of either the engulfed cell or the "host" cell.

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* * *

Dr. Cline Responds:

TO THE EDITOR: Although other nucleated cell forms are occasionally found within the cytoplasm of megakaryocytes, this phenomenon does not truly represent phagocytosis. Rather, it indicates that cells have migrated up the small demarcation channels which run through the cytoplasm of the megakaryocyte. Phagocytosis, on the other hand, is an active process by which the phagocytic cell surrounds the particle with its cytoplasmic membrane ultimately enclosing the particle in a cytoplasmic vacuole.

Both phagocytosis and the process by which nucleated cells enter megakaryocytes may result in an "internalized" cell surrounded by a halo when viewed by light microscopy. Light microscopy, therefore, cannot distinguish these two processes. It is generally thought that emperipolesis and true phagocytosis can be distinguished by the electron microscope. From the evidence we have available, it is impossible to state whether the cells we observed in our patient with chronic myelocytic leukemia in blast crisis were megakaryocytes. Dr. den Ottolander's view is interesting, but not conclusive.

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Refer to: Gerber WG, Massad RJ: Training physicians for primary care: Trends and hazards (Medical Education). West J Med 127:426-432, Nov 1977

Training Physicians for Primary Care: Trends and Hazards

WILLIAM G. GERBER, MD, *San Francisco,* and ROBERT J. MASSAD, MD, *Iowa City*

Programs to train physicians more effectively for careers in primary care are being organized within academic departments in internal medicine and pediatrics, while the number of training programs in family practice continues to grow rapidly. However, the field of primary care training is expanding without a common vocabulary and with inadequate communication between the specialties involved.

If decisions concerning health care policy are to be made rationally, the development of multiple distinct models for primary health care delivery must be encouraged and these models must then be evaluated.

The distinction between family practice and family medicine must be made clear if the latter discipline is to realize its potential application to all specialties.

The relative exclusion of family practice from universities and the absence of experienced practitioners in university primary care programs are conditions that threaten the future of both types of programs and deserve thoughtful attention from medical educators.

IT APPEARS that America's system of medical education has begun to address purposefully the problem of meeting this country's need for primary health care. In frequent contributions to the recent medical literature[1-5] and at a succession of national conferences, representatives from internal medicine and pediatrics have discussed strategies to prepare their trainees more effectively for the practice of primary care. Programs for this purpose have recently been established in a number of our medical schools with the support of the federal government and private foundations. Along with this development, graduate training programs in family practice have experienced a growth that not even the specialty's most ardent supporters could have predicted when it was established in 1969.

Petersdorf[6] recently has described the present state of physician maldistribution in the United States, which he ascribes to a lack of planning, coordination and control over the growth of specialties in the past 30 years. There are indications that the field of primary care will replicate that unplanned growth. The primary care movement

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is growing rapidly without a common vocabulary and with minimal communication between the specialties involved. Rather than a coordinated effort to train sufficient numbers of physicians for primary care careers, the field has divided into fractions which at best ignore and at worst compete with each other.

The purpose of this article is to briefly review the history of the growth of the primary care movement in this country; to offer some definitions of terms which may begin to provide us with a common vocabulary; to describe the major models of primary care training being developed; to outline some current trends which we believe must be reversed, and to make several recommendations for the field.

Background

Two documents—The Millis report[7] and the Willard report[8]—are important reference points in the history of the primary care movement in the United States. In 1966 the Citizens Commission on Graduate Medical Education, chaired by John S. Millis, PhD, presented its recommendations. Among them was the establishment of a new specialty to train primary physicians in the continuous, comprehensive care of families.

In 1964 the Council of Medical Education of the American Medical Association appointed the Ad Hoc Committee on Education for Family Practice, chaired by William R. Willard, MD. The findings of the committee were summarized in the Willard report, issued in 1966. It held that family practice was a viable primary care model and that "major efforts should be instituted promptly to encourage the development of new programs for the education of large numbers of family physicians" through the development of new sources of funding and the conferring of specialty status on the discipline. It also urged that "medical schools and teaching hospitals . . . explore the possibility of developing models of family practice, in cooperation with the practicing profession."[8]

By the mid-1960's, legislative and funding bodies began to express interest in promoting and supporting primary care. This interest was followed by the establishment of the American Board of Family Practice and the conferring of specialty status on general practitioners in 1969. Funds were made available from state, federal and private sources for establishing training programs in the new specialty. The resulting increase in the number of family practice programs and their graduates is impressive: in July 1969 there were 20 family practice residency programs; in July 1976 there were 293.

Until recently, therefore, family practice has represented the major thrust in the movement to train primary care physicians in the United States.

Although the number of postgraduate training programs in family practice has increased dramatically, the specialty is only beginning to make its presence known in undergraduate medical education. In July 1976 more than 25 American medical schools reported that they had no department or division of family practice. Of the 79 departments in existence, 13 were less than a year old. This relative absence of academic family practice can be partially explained by its unorthodox manner of development. Most specialties evolve slowly from within the profession as new, research based, narrow fields of expertise practiced by a few physicians located primarily within universities. The specialty of family practice arose comparatively abruptly, as a result of societal and legislative pressure, and represented a broad area of medicine which had long been practiced by a large segment of the profession based outside universities. So when the new specialty was established in 1969 it lacked a solid base in academic centers on which to build its research and teaching activities.

As our medical schools have explored the potential establishment of departments of family practice and family practice residencies, they have faced major obstacles. The first has been the problem of faculty recruitment. Universities have been forced to recruit most family practice faculty members from the ranks of practicing physicians. This situation has been difficult because traditional criteria for appointment of medical school faculty fit the majority of family practice candidates poorly. Few have been university-trained; many are former general practitioners whose formal training consists of an internship years before. Few have published, fewer still have done research. Many have taught, but usually in peripheral capacities, such as office preceptorships. To start such a person at an academic rank and salary competitive with the rewards of practice requires making clinical experience equivalent to activities in research, teaching and publishing for purposes of appointment and promotion.

In short, the political realities of university procedure and the very small number of traditionally

suitable candidates for faculty positions have resulted in the specialty of family practice having limited representation in universities. The family practice movement consequently is the first major development in American medical education that has occurred outside of our universities since the Flexner report of 1910.

The focus of primary care training might have remained extramural indefinitely, were it not for the fact that some of the most respected personalities in medical education have continued to urge our medical schools to take the lead in educating physicians for primary care. The Pellegrino report to the Executive Committee of the Association of American Medical Colleges in 1968 echoed the Willard report in urging that medical schools assume a central role in the "redefinition and rehabilitation of the role of the general physician."[9] Hillard Jason and other medical educators have pointed out that medical schools focus on secondary and tertiary care, while most of their graduates end up doing primary care.[10] In *The Education of Physicians for Primary Care,* an important and thoughtful document, Alpert and Charney[11] put it succinctly:

> It would seem that Pediatrics and Internal Medicine need to reach some rational decisions in relation to family practice. Either they ought to relinquish their role in primary care education and practice—and also recruit proportionately fewer medical graduates to their own fields—or else acknowledge their own obligations to primary care and reassess their educational efforts with this in mind. To continue to recruit the majority of medical students without accepting the fact that most of them should be prepared largely to practice primary care strikes us as almost unethical, given our current shortage of primary care physicians.

In addition to this intellectual prodding, a second factor which has shifted the attention of our medical schools to primary care has been the increasing number of medical students applying for family practice residencies. In 1976 more than 2,500 graduating students applied for the approximately 1,935 available first year positions. Many are outstanding students who are choosing family practice because it is their only opportunity for graduate training in primary care. They represent an attractive pool of applicants for university training programs in the traditional specialties which can be captured only if their needs for primary care training can be met in those settings.

Third, and maybe most important, there has been financial pressure on the medical schools for the development of primary care training. Since the late 1960's financial support of the basic science research structure and, thereby, much of the medical school faculty, has been shrinking. At the same time, federal, state and private agencies have become more willing to fund research and training in primary care.

Faced with the alternative of abandoning the primary care field to family practice or developing primary care programs more compatible with their own goals and needs, it is understandable that our medical schools have not universally accepted the concept that internal medicine and pediatrics should relinquish their role in primary care education.

Following a flurry of conferences in the primary care field in the last few years encouraging their development, residencies in internal medicine and pediatrics have begun to appear which are specifically designed to prepare their graduates for careers in primary care. These programs differ from family practice residencies in two important aspects. First, they are all within medical school systems. Second, they are being organized within or closely allied to already existing departments in the medical schools.

At present, then, family practice programs are growing rapidly, but primarily apart from universities, while primary care programs in internal medicine and pediatrics are being established almost exclusively within our medical schools. Therefore, we are witnessing a two-pronged movement in primary care training.

Definitions

Primary care, family practice, general practice and family medicine are terms that are being widely used without general agreement about what they mean. Thus far in this discussion we have not been concerned with their precise meanings. However, if we are to avoid false issues and effectively address real ones, we must start with a common understanding of these terms.

For the remainder of this discussion, the following definitions will be used:

Primary care has been referred to as primary medicine and given a three-part definition by Alpert and Charney:

> Primary medicine is first-contact medicine . . . Primary medicine assumes longitudinal responsibility for the patient regardless of the presence or absence of disease . . . Primary medicine serves as the "integrationist" for the patient.[11]

Family practice is primary care delivered by a

physician in multiple specialty areas to people of all ages and both sexes. Several authors have addressed themselves to the distinction between general practitioners and family practitioners;[13-15] our emphasis would be on the specific training in primary care given to the latter.

Family medicine has been well defined and defended by Ransom and Vandervoort[16] as a distinct academic discipline. In their words:

> Family medicine is an emerging discipline concerned with the relationship of life in small groups to health, illness and care. Its focus is on the ecology of relations among individuals in families and between families and their surrounding environment. (This term family is used in the broadest sense to describe any group of intimates with a history and a future.) Family medicine aims toward understanding and changing health problems that cannot be managed successfully by dealing exclusively with the individual and his or her illness, abstracted from the pattern of recurrent interpersonal situations that shape and transform a human life.

Family health care is primary care delivered by a health professional to people of all ages and both sexes in the context of a family systems approach. It implies that the practitioner is grounded in the discipline of family medicine and applies its principles to his practice. Janeway[17] has said it is "based . . . on family medicine, focuses on the family, and is an attempt to combine health promotion and illness care for the family."

Training Models

Having reviewed the growth of family practice programs and the recent development of primary care programs, we will now describe the training models being utilized by these programs.

Among the primary care programs being established, several different models appear to be emerging. The first type can be labeled the *single-specialty* model. This type of program is a residency in either internal medicine or pediatrics which has an emphasis on primary care and whose graduates will be board eligible in one or the other specialty. The training is of the traditional length but with an emphasis on outpatient medicine. Presumably, a graduate of such a program has received training more relevant to a primary care practice than his traditionally trained counterpart.

The second model of primary care training that we have identified is the *team* model in which residents in internal medicine and pediatrics are trained to work together in the delivery of primary health care. The residents are scheduled to be in the ambulatory facility together and training includes attention to the principles of teamwork and collaboration.

The third identifiable model produces a graduate trained in at least two specialty areas of primary care. This *multispecialty* model presents two distinct variations. In the first, the resident is trained in internal medicine and pediatrics. In one such program the resident "majors" in one specialty and "minors" in the other. The graduate is board eligible in his "major" and is expected to serve as a generalist in that specialty, taking care of both ambulatory patients and those requiring hospital care. He is expected to practice ambulatory primary care in his "minor" and to be competent to care for most of the problems of that specialty area.

The second *multispecialty* model adds to the resident's training in internal medicine and pediatrics outpatient skills in other specialty areas such as orthopedics, gynecology, dermatology and the like. Again, depending on whether the "major" has been in the area of internal medicine or pediatrics, he is board eligible in that specialty at the conclusion of this program. Compared with the single specialty model, both of these programs might be expected to produce a graduate who sacrifices depth of knowledge for breadth of practice. Some of these programs attempt to compensate for this additional breadth by extending the duration of the residency one year.

The fourth distinct model of primary care training programs is *family practice*. As with primary care programs, there are differences between family practice residencies. However, all family practice programs share certain basic elements. Important among these is the requirement for a Family Practice Center in every program. A family practice resident spends a substantial portion of his or her time in the model unit, caring for patients in a continuing relationship and taking care of most of their health needs. Generally, this outpatient time grows from 10 percent in the first year to 50 percent in the third year, with time alloted weekly over the three years to assure continuity. The amount of time spent on other specialty services varies between programs but there are established minimums for internal medicine and pediatrics. In addition, family practice residencies are similar in their commitment to teaching the resident skills in other specialty areas which include outpatient orthopedics; ear, nose and throat; ophthalmology; gynecology, and ob-

stetrics. The graduate of a family practice residency is a primary care specialist expected to be capable of caring for most of the health needs of a patient population of all ages and both sexes.

The fifth and last primary care training model to be discussed is *family health care*. All of the programs previously outlined could, with the addition of family medicine to their curricula, be described as family health care programs. The unfortunate reality is that few programs teaching primary care teach family health care. There are many reasons for this, prominent among which is the infancy of the discipline of family medicine. Few of the professionals who have directed their attention to the interaction between the family and health and illness patterns can apply this knowledge at the level of patient care and thereby make it a valuable curricular addition to a residency training program. The net result is that relatively few primary care or family practice programs teach family health care. Happily, both family practice and the newer primary care programs are experimenting with the application of family medicine to primary care delivery and we are hopeful that this area will be vigorously explored.

Current Trends

We have reviewed the recent growth of the primary care movement in this country, defined some of the terms which are identified with it and outlined the most common models of primary care programs in this country. We will now examine two of the trends in the movement and discuss some of their potential consequences.

There is widespread terminological confusion in the primary care field. If we are to develop a rational, economical primary health care system for this country, we must encourage the development of distinct models of primary care delivery and then evaluate their comparative effectiveness. But we can do neither if we do not carefully define the models and understand their similarities and differences.

The immediate danger of the existing confusion is that funding agencies share the mystification which has occurred and that funds meant to stimulate innovation are in fact supporting traditional models. Analysis of certain primary care programs, for example, shows an emphasis on ambulatory care with major concentration in medicine and pediatrics and minor exposure to training in office gynecology, orthopedics and minor surgical procedures. We question the difference between the graduate of such a program and the graduate of a family practice residency and wonder why it should be supported as an innovative experiment in medical education?

The more far-reaching danger is that we will not evaluate these models adequately. There are questions to be answered that are of overwhelming importance to the establishment of a rational health policy. The validity of the evaluation depends on acknowledging of the differences that exist between the various delivery models. How does an internist-pediatrician team compare with a family physician? What is the cost effectiveness of each approach? Does significant and sufficient communication take place between teammates and is the relationship with the family better or worse than if a single physician fills both roles? Does this last question matter? Are there benefits in the greater depth of training of the internist and pediatrician and how do these affect quality of care and costs compared with the breadth of training of the family physician? In order to obtain valid answers to these and many other pressing questions, the models to be evaluated must be clear and distinct.

The lack of a clear terminology also threatens the future of family medicine and family health care. To the extent that both remain synonymous with family practice they will not receive adequate recognition or support, nor can they be fairly evaluated.

Family medicine is a theoretical perspective and a body of knowledge with potential application to any medical practice. It places the patient in the context of his environment, puts the medical intervention in a broader perspective, and expands the diagnostic and therapeutic possibilities of the physician to include the impact of the family on the disease process and the impact of the therapy on the patient's support system. It is as valid to a surgical subspecialist as it is to a primary care physician. As such, it deserves a prominent place in the undergraduate medical curriculum as a part of the knowledge base utilized by all clinicians. It also deserves support so that its academic base and its clinical application can be expanded.

Family health care is the application of family medicine to the care of families. It is not the sole domain of the family physician, but can be provided by other primary care providers or teams who care for all family members. It is our hypoth-

esis that the addition of a family medicine perspective to a primary care practice results in a measurable difference in the style and outcome of the practice. However, until family medicine and family health care are distinguished from family practice, this hypothesis cannot be widely explored.

The second trend which requires comment is the two-pronged nature of the primary care movement in this country. Family practice residency training is located predominately in community hospitals while the development of residencies in primary care has occurred within the university setting. We are concerned about both elements of this movement.

The success of family practice at this time is measured primarily by the growth in the number of residencies, the large number of highly qualified applicants seeking admission to those programs, and the financial support which family practice has received from various agencies concerned with the deficit in primary care physicians. However, unless it develops strong university programs, this success may be transient. As alternative solutions to the primary care shortage are offered by the medical schools, funds will almost certainly be diverted to those programs. As they become available, the medical students who now see family practice as their only viable choice for a career in primary care may also be diverted. Neither of these consequences will result from the proven advantage of one model over the other, or even from the higher quality of one form of training over the other. They will occur naturally if role models for primary care exist within the medical school and similar exposure to family physicians does not.

If family practice is to become a fully accepted specialty within our medical schools, attitudes of existing faculty must change and academic family practice must recognize its responsibility in promoting this change. Every specialty has an area of expertise which it is obliged to refine and develop and family practice is no exception. The new specialty is faced with a challenge: to prove and delineate its area of expertise; to teach its skills; to develop its research base. If this does not occur, family practice will contribute to its own demise in the academic setting and its full potential as a viable form of primary care will never be realized.

Our second concern about the split in the movement is that primary care may not be taught at all in university-based programs in internal medicine and pediatrics. Primary care is a specific style of practice that incorporates skills that are not being taught in traditional residencies in internal medicine and pediatrics. However, those responsible for the establishment of most of the emerging primary care residencies in this country are traditional academicians who have had no practice experience; or, if they have, it has not been in primary care. Many of the faculty members of these programs are being recruited from within the medical schools, merely moving from one funding source to another with a change of title but no change of perspective. Consequently, students and residents may be taught primary care by persons with no experience or expertise in the field. It is possible that they may not be taught primary care at all, but merely take a traditional medical or pediatric residency, with more time allocated to outpatient care, when little or no teaching takes place.

If this trend continues and university-based primary care programs do not develop faculties in which there is experience, skill and interest in primary care, primary care physicians will not be produced in our medical schools, and medical schools will not participate in the evolution or growth of primary care in this country. This would obviously be a serious setback to the primary care movement.

Recommendations

- Those responsible for financial encouragement and ongoing support of primary care programs must make their investments carefully. It is their responsibility to ensure that they are in fact supporting true primary care programs, and to look closely at the models they are considering to encourage real diversity.
- Thorough understanding and acknowledgment of the various models of primary care must take place. This is an essential step if we are to evaluate the different variables between models and plan effectively for the future.
- Family medicine must gain the recognition and interdisciplinary support it needs to develop as a new academic field and it must be shown that the family health care model which results from its application to primary care is a significant variable.
- Family practice, especially those programs in academic settings, must generate a research base which will show clearly those unique areas

of knowledge and skill which make it a specialty.

- Primary care programs in the university must prove their commitment to producing real primary care practitioners by recruiting faculty members with extensive primary care experience.
- The university must adopt new standards for faculty appointment and promotion which recognize skill in teaching and patient care.

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Nonindications for Inhaled Corticosteroids in Asthma

Obviously, inhaled corticosteroids should not be introduced in a patient whose airway is obstructed. . . . When a patient has an obstructive bronchial disease, you have to clear the airway before the drug is introduced. Day-to-day adjunctive therapy should be given and it is unwise to use these drugs unless alternative treatment programs have significant disadvantages because we don't know the long-term effects of inhaled steroids on the bronchial tree. It is not recommended for an asthmatic patient who has only infrequent, moderate-to-severe flareups of asthma. In this instance, bronchodilators, fluids, short-burst steroids—preferably prednisone—will usually reverse the disease. They are not that effective for exercise-induced bronchospasm and there is even some indication . . . that they may not be particularly effective for severe pollen-induced, self-limited, seasonal asthma. For exercise-induced bronchospasms, cromolyn or theophylline, or both, are probably better to use.

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A University/Community Hospital Family Practice Residency Program

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A residency program associated with a major university has many obvious advantages. On the other hand, a residency program located in an area of health manpower shortage is a major advantage to that community. This paper describes the development of a university affiliated family practice residency in the Mojave Desert of Southern California. It reports that it is possible to form a successful alliance between a medical center and a rural community, bringing increased primary care to the community, upgrading the quality of medicine practiced in the community and augmenting the staff of the local hospital without sacrificing training for the family practice residents. Furthermore, the residency program can become financially self-sufficient.

SINCE THE PUBLICATION of the Willard report[1] and the Millis report[2] in 1966, followed in 1968 by the approval of the *Essentials of Residency Training in Family Practice* by the House of Delegates of the American Medical Association, there has been increasing interest in the development of training programs in family practice. Recent statistics published by the American Academy of Family Physicians (AAFP) indicate that the number of approved residency programs has grown from 30 in 1969 to 288 in 1976. Student interest has increased the number of residents from 290 in 1970 to 4,675 in 1976.[3]

Recommendations for the development of a family practice residency program have generally appeared as supplementary pamphlets[3-5] or workshops.[6,7] This paper outlines the steps taken in establishing a family practice residency program in a health manpower shortage area. The program is, at the same time, integrated with the University of California at Los Angeles (UCLA) School of Medicine, bringing with that affiliation the in-depth teaching that can come only from a university center.

The High Desert

The Antelope Valley Hospital Medical Center is a 184-bed acute care hospital located in Lancaster, a rural, unincorporated community in the Mojave desert of California. Two major problems relating to health care delivery had long been apparent to the administration and medical staff of the hospital. First, there was a severe shortage of physicians providing primary care to the community and, second, there was a chronic need for an ongoing program of continuing medical education to maintain and upgrade the quality of health care delivered in the community.

Recognizing that a family practice residency training program at their hospital could provide the vehicle both for introducing potential family

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physicians to the community[8,9] and for developing an ongoing program in continuing medical education, the hospital administration conducted a feasibility study which led to the development of an approved residency training program.

Phase I—Commitment

The first step was the appointment by the chief of staff of a Family Practice Residency Planning Committee consisting of the hospital administrator, the director of nursing services, the chiefs of all clinical departments, and a physician to serve as a liaison between the hospital and the university medical school. This committee was charged with the responsibility to study the *Essentials of Residency Training in Family Practice* and to present to the board of directors the educational, financial and administrative commitment necessary for the development of a family practice residency program.

Educational Commitment

It was recognized that the primary goal of the proposed training program should be a commitment to education rather than service to the hospital. It was therefore necessary to establish the identity of family practice as a clinical specialty and to develop a commitment to teaching from the medical staff.

A separate family practice clinical service was designated and included within the medical staff organizational structure. A plan was drawn up to establish ongoing teaching conferences utilizing various members of the already existing clinical departments. Further, the various services agreed to commit teaching cases to the residency program for which the resident would be responsible.

Potential voluntary faculty members were identified from the hospital staff who would teach both in the hospital and in the future Family Practice Center. These faculty members gave ample commitment to voluntary teaching; nevertheless, because this was an area of health manpower shortage, they already were overextended. It was realized that a full-time faculty of two family physicians, a pediatrician and an internist would be needed to provide a quality longitudinal educational curriculum.

A program of continuing medical education was instituted within the hospital under the direction of a salaried director of medical education. The responsibilities of the director of medical education were to develop:

- an ongoing program of continuing education,
- a process of patient care evaluation that would identify the empirical evidence of educational needs within the medical community,
- educational facilities in which to conduct the continuing medical education activities,
- a patient education program,
- community health education programs and
- a continuing education program for nursing and allied medical personnel.

The medical staff gave its strong commitment to the support of the educational requirements of the program and referred four major recommendations to the hospital board of directors:

- the priority of education over service,
- the employment of a full-time family practice faculty,
- the establishment of a continuing medical education program and
- the employment of a full-time director of medical education.

Financial Commitment

The Residency Planning Committee advised the board of directors of the hospital that a potential expenditure of $40,000 per resident per year was probable. This included costs of operating a Family Practice Center and the salaries of residents and full-time faculty. They were encouraged to commit themselves to total support, not relying on grant funding, and to ongoing support, to guarantee the program's viability and to attract outstanding full-time faculty candidates.

Armed with this information, the hospital administration and board of directors conducted a fiscal feasibility study to determine the financial needs of the program and to identify sources of funds from within the existing hospital budget. They were informed that the development of this program would postpone or eliminate the consideration of several new budgetary items within each department. It was, however, with firm departmental support that the board of directors committed itself to support of the fiscal needs of the Family Practice Residency Training Program.

The feasibility study further indicated that the Family Practice Center could be self-supporting in three years, utilizing the concept of faculty and residents practicing together as a group.

Administrative Commitment

The hospital administration was advised that administrative assistance to the Family Practice

TABLE 1.—*Number of Admissions per Major Department*
(For fiscal year ending June 30, 1974)

Newborn admissions	1,034
Medical admissions	1,911
Surgical admissions	1,964
Obstetric admissions	1,147
Pediatric admissions	634
Mental health unit admissions	573
TOTAL ADMISSIONS	7,263

Residency Program would be required in the form of a full-time business manager and staff, to free the future program director from as much administrative responsibility as possible. Support was also requested from the hospital comptroller, purchasing director and directors of other supporting departments. The administration agreed to provide this assistance, and yielded decision-making autonomy in the day-to-day operation of the Family Practice Center to the family practice faculty.

With the educational, financial, and administrative commitments defined and accepted by the medical staff, the board of directors, and the administration, phase II was initiated.

Phase II—Planning and Development

The Family Practice Residency Planning Committee, expanded to include the new director of medical education, amassed and studied all information on family practice training programs available from the American Board of Family Practice, as well as selected literature[1-6] recommended by the UCLA Division of Family Practice. Several site visits were made by committee representatives to established family practice residency training programs to help the committee better understand the Family Practice Center operation and inpatient rotations. A representative was also sent to Kansas City to attend the 1975 AAFP Annual Workshop for Developing Programs; this was perhaps the single most informative activity of the planning and development phase.

During this phase a detailed analysis of the clinical volume of each of the major services of the hospital was conducted to determine the actual patient exposure available to trainees in terms of demographic and disease distribution in the hospital in the preceding three years. A study of the activity of the emergency room was also conducted, taking into account both medical and surgical emergencies (Tables 1 through 3).

Concurrently, the hospital administration selected a site in a new medical office building adjacent to the hospital for the Family Practice Center and began architectural plans for its development. The initial three-year budget for the family practice training was developed. The final aspect of phase II was the recruitment and em-

TABLE 2.—*Discharge Analysis of Hospital Service*
(For fiscal year ending June 30, 1974)

Service	Total Number of Discharges	Ages 0-13	Ages 14-64	Ages 65+	Total Hospital Days	Average Length of stay	Cons	Op	Deaths	Inf	Pediatrics Number M	Pediatrics Number F	Pediatrics Hospital Days	0-13 Average Length of Stay
Medical	1,571	269	717	585	12,733	8.1	187	0	87	10	172	97	1,137	4.2
Surgical	627	73	416	138	3,999	6.4	28	497	34	18	45	28	183	2.5
Traumatic	521	92	347	82	4,160	8.0	128	316	17	6	67	25	356	3.9
Ear, nose and throat	236	116	112	8	533	2.3	11	207	1	1	58	58	185	1.6
Eye	202	34	90	78	803	4.0	4	206	0	0	18	16	72	2.1
Urology	293	31	168	94	2,169	7.4	81	214	13	2	20	11	100	3.2
Orthopedics	257	16	195	46	1,674	6.5	35	170	1	7	11	5	46	2.9
Oral surgery	11	1	10	0	36	3.2	0	10	0	0	1	0	1	1.0
Neurology	296	9	248	39	2,166	7.3	132	97	4	9	5	4	59	6.6
Obstetrics														
Delivered	1,045	0	1,045	0	2,636	2.5	10	90	0	1	0	0	0	0
Not delivered	83	0	83	0	140	1.7	3	5	0	0	0	0	0	0
Aborted	206	0	106	0	210	2.0	4	93	0	0	0	0	0	0
Gynecology	324	2	307	15	1,789	5.5	22	314	2	6	0	2	7	3.5
SUBTOTAL	5,572	643	3,844	1,085	33,048	5.9	645	2,219	159	60	397	246	2,146	3.3
Psychiatry	652	6	622	24	7,115	10.9	96	5	3	3	3	3	92	15.3
TOTAL	6,224	649	4,466	1,109	40,163	6.5	741	2,224	162	63	400	249	2,238	3.4
Newborn	1,037	1,037	0	0	3,033	2.9	19	1	9	0	0	0	0	0
GRAND TOTAL	7,261	1,686	4,466	1,109	43,196	5.9	760	2,225	171	63	400	249	2,238	3.4

Cons = consultations
Op = operations
Inf = infection rate

TABLE 3.—*Emergency Room Statistics*
(For fiscal year ending June 30, 1974)

Total emergency room admissions	16,423
Average number of patients seen per day	45
Number of patients seen on weekends (Saturday and Sunday)	5,724
Average number of patients seen on each two-day weekend	110

Number of patients seen for three-month period, 6:00 PM to 8:00 AM

1974	*Per Month*	*Average per Day*
June	808	26
July	788	25
August	780	25

Number of patients seen on holidays	
New Year's Day, January 1	39
Lincoln's Birthday, February 12	42
Washington's Birthday, February 18	58
Memorial Day, May 27	62
Flag Day, June 14	45
Independence Day, July 4	50
Labor Day, September 2	74
Columbus Day, October 14	54
Veteran's Day, October 28	49
Election Day, November 5	28
Thanksgiving, November 28	43
Christmas, December 25	34
TOTAL	578
AVERAGE PER DAY	48

administration of a private group practice of medicine which the Family Practice Center was to simulate.

Phase III—Affiliation With a Medical School

During phase II the Residency Planning Committee realized that affiliation with a university department or division of family practice would provide several benefits to the community hospital training program:

- advice in curriculum development, implementation and evaluation;
- support for faculty recruitment, training and evaluation;
- guidance in the development and evaluation of research programs;
- access to a visiting professor program;
- utilization of university education resources —library, audiovisual and the like;
- increased potential for resident recruitment, and
- pooled experience with other affiliated programs.[3]

The Division of Family Practice at the UCLA School of Medicine was asked to consider such an affiliation. The hospital's commitment to the program was clearly proved to the division through its efforts in developing phase I. Having carefully reviewed the statistical analyses (Tables 1-3), the Division of Family Practice determined that the clinical volume appeared to be insufficient to support a full three-year training program at a single site; it therefore recommended an integrated program with the UCLA School of Medicine. The final plan called for the first year of residency training to be taken within the UCLA training facilities in order to provide a strong, traditional academic grounding in medicine, pediatrics, obstetrics, surgery and dermatology, as well as a full year's family practice training in the UCLA Family Practice Center. The second and third years of training would be spent in what was felt to be an excellent experience in a community-oriented facility at the Antelope Valley Hospital Medical Center. This concept was accepted by the Residency Planning Committee, and a full three-year integrated curriculum was developed. A search committee was formed with the UCLA Division of Family Practice to identify a program director and full-time faculty members. Phase III concluded with a formal association agreement with the Division of Family Practice at the UCLA School of Medicine.

Phase IV—The Application Process

An application to the Family Practice Residency Review Committee was obtained from the Division of Graduate Medical Education of the American Medical Association and a rough draft developed with the aid of the UCLA Division of Family Practice. Consultation with a representative of the AAFP Commission on Education provided the hospital with an objective critique of its plans for the development and implementation of the curriculum. Recommended modifications were made and the formal application was submitted to the Family Practice Residency Review Committee for consideration in August 1975. Approval was received in December of that year to train a total of 12 residents, four in each year of training. The total length of time elapsed from the formation of the Family Practice Residency Planning Committee to the approval of the formal application was 16 months.

The residents now in training are each responsible for the care of six to eight patients per day on each of the clinical inpatient services. The faculty felt that fewer patients would not provide an

adequate teaching exposure, and more would increase the workload beyond the point of maximum learning. Studies are in progress to test this hypothesis and establish optimum patient volume in each year of training. Research is also being conducted to measure the development of a patient population and the financial status of the Family Practice Center. These data will be collected and assessed for publication after a full year of operation.

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Antacid Therapy and Recurrent Ulcers

IS THERE ANY evidence that continuance of antacid therapy after an ulcer has healed is of any value?

DR. ISENBERG: The problem is patient compliance. There have been a number of studies showing that patients in a hospital—even bleeders—do not take antacids. . . . There is no strong evidence indicating that antacids prevent complications or recurrences—but, then, patients probably do not take them. I think the evidence suggests that antacid therapy does have an effect and I recommend that patients with duodenal ulcers take about 120 mEq of neutralizer, such as 30 ml of Mylanta®-II (aluminum hydroxide, magnesium hydroxide and simethicone) one and three hours after each meal and before bed—that is, seven doses a day. But won't patients get terrible diarrhea from that much Mylanta II? . . . That doesn't occur.

DR. OWENS: There are studies that do show that treatment with anticholinergics continued after an ulcer is healed does diminish the frequency of recurrences. Notice I did say "diminish." . . . Telling what I would do if I had an ulcer would be the best way to give my opinion. . . . I would probably stop taking antacids some time after the ulcer was completely healed. I would continue taking a anticholinergic at bedtime, probably for several years if I had repeated ulcers. The average time that the patients we see have had an ulcer is eight years, according to one study done some time ago. The study showed an average of eight recurrences, and, therefore, the ulcers were already chronic. I think, in that setting, I would take anticholinergics regularly for at least several years to try to prevent recurrences. And, incidentally, I would be sure that if I was taking an anticholinergic along with an antacid that I took them at separate times because antacids bind anticholinergics; that is one of the reasons why they're relatively ineffective in some people. Finally, . . . the effect of antacids varies from person to person and so do anticholinergics. And if you don't give a dosage up to the point of causing some slight side-effects, then you're not giving enough.

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JON I. ISENBERG, MD, *Los Angeles*

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Refer to: Regardie AG: If unprofessional conduct is charged by the California Board of Medical Quality Assurance (Medical Jurisprudence). West J Med 127:438-441, Nov 1977

If Unprofessional Conduct Is Charged by the California Board of Medical Quality Assurance

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The right of a physician to practice his or her chosen profession must be balanced against the right of the public to be protected from unprofessional conduct by physicians. By providing notice and a hearing before imposing discipline, if any, on a physician for unprofessional conduct, the California Board of Medical Quality Assurance meets the basic requirements of procedural due process. However, although the constitutional rights of the physician may be protected in this way, the administrative disciplinary process itself is likely to be an arduous experience. A basic understanding of the nature and legal effect of such disciplinary proceedings may assist a physician in defending against the charges.

THE PURPOSE of this article is to provide an overview of what may be expected if disciplinary charges are brought against a physician for unprofessional conduct by the California Board of Medical Quality Assurance (referred to in the article as the Board). While it is beyond the scope of the article to treat this subject in detail, it is intended to provide some insight into the nature and legal effect of these proceedings so that the physician may be better prepared to defend against the charges.

Commencement and General Nature of Board Proceedings

A Board hearing to revoke or suspend a physician's license for unprofessional conduct is initiated by the filing of an accusation by the Board against the physician. The Board has broad powers to investigate information received from all sources concerning purported unprofessional conduct by a physician. In this regard, under California law, settlement of any malpractice suit against a physician involving payment by the physician's insurance company to the plaintiff of more than $3,000 must be reported by the insurance company to the Board. Thus, settlement of a civil suit for malpractice against a physician may not end the disquieting experience for the physician because the Board may conduct its own independent investigation, based on information received from the insurance company, and thereafter commence disciplinary action.

In California, hearing procedures to be followed where the suspension or revocation of a physician's license is contested are prescribed by the Administrative Procedures Act (referred to here as the Act). Proceedings under the Act may generally be divided into two classifications: (1)

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proceedings relating to the denial of an application for a license and (2) disciplinary proceedings, which relate to suspension or revocation of a license for unprofessional conduct.

A hearing before the Board is similar to a nonjury trial in a civil case in that it is a contested adversary proceeding. However, in contrast to a civil court trial where the judge who hears the case often decides it, the Board, which often does not hear the case, decides it. Disciplinary proceedings are usually heard by a hearing officer who submits his proposed decision to the Board. The Board then renders its decision based on the pleadings and the record of proceedings before the hearing officer.

Although the hearing is conducted by a hearing officer, the Board itself may decide to hear the case together with the hearing officer, in which event the Board and the hearing officer divide the functions and conduct the hearing. In such an event, the Board in a sense is exercising the functions of both prosecutor and judge. Despite an apparent conflict of interest, such an arrangement, under California law, has been held not to deprive the physician of due process.

Parties to administrative proceedings are entitled to a fair hearing, which includes the right to be heard by an impartial tribunal. Should a physician feel any member of the Board is biased, the physician may attempt to disqualify that member from participating in the decision of the Board. This must be done by filing a motion to disqualify the Board member, supported by affidavits, as soon as the bias is discovered.

Closely related to the question of Board bias is the question of Board expertise. It is improper for a Board member to rely on his own opinion as evidence when he has not testified as a witness and thereby provided the physician with the opportunity through cross-examination to test the basis for his opinion. Therefore, for example, a Board member cannot conclude on the basis of his own knowledge that a drug is dangerous without evidence presented to that effect.

In California there is a liberal application of the rules of evidence in any administrative disciplinary proceeding. Under California law,

> . . . [a]ny relevant evidence shall be admitted if it is the sort of evidence on which responsible persons are accustomed to rely in the conduct of serious affairs, regardless of the existence of any common law or statutory rule which might make improper the admission of such evidence over objection in civil actions.

Comparison of Board Proceedings and Criminal Proceedings

Board proceedings have been held to be civil rather than criminal in nature since they are designed to protect the public rather than punish the physician. Nevertheless, there are some rather interesting comparisons in Board proceedings to criminal cases. For example, the California Supreme Court recently held that the defense of entrapment (which is, generally speaking, the State's procurement of an innocent person to commit a crime) is always available in an administrative proceeding. This decision may well point the direction the court may take on the question of whether illegally obtained evidence is admissible in an administrative hearing. Therefore, it is possible that a statement made by a physician to an investigator, where the physician has not first been advised of his constitutional rights, may not be admissible against him in a subsequent disciplinary hearing. However, the physician should make no statement to the investigator, even if he is advised of his rights, without first consulting with his attorney.

Additionally, since an administrative proceeding is not a criminal case, a physician may be compelled to take the stand and be sworn as a witness, in contradistinction to a defendant in a criminal case who has a constitutional privilege not to be called as a witness. Having taken the stand, however, the physician may on proper grounds decline to answer any question that may tend to incriminate him or her since the privilege against self-incrimination applies to civil as well as criminal proceedings.

As in criminal cases, the physician-patient privilege is not available to the physician in administrative disciplinary proceedings.

A conviction in a criminal case based on a plea of nolo contendere may not be used in a subsequent civil action and, hence, may not form the basis for disciplinary action. Similarly, a physician's conviction on a nolo contendere plea of misdemeanor drunk driving may not be the basis for revoking his certificate to practice medicine for a conviction involving the use or consumption of alcoholic beverages. It should be noted that the question of whether a conviction involves moral turpitude (generally, moral turpitude includes acts of fraud, intentional dishonesty, and acts of baseness, vileness or depravity), so as to warrant revocation or suspension of the physi-

cian's license to practice medicine, cannot be determined in the abstract but depends rather on whether the conviction itself shows there to be unfitness to practice medicine. The State's power to regulate the medical profession cannot be used arbitrarily to penalize conduct having no demonstrable bearing on fitness for its practice. Thus, for example, a conviction of willfully residing in a house of ill fame, if based on circumstances of personal residence wholly unrelated to medical practice and only peripherally related to prostitution, would not show professional unfitness on account of baseness, vileness or depravity.

Acquittal or dismissal of criminal charges is not a bar to subsequent disciplinary proceedings.

Determination of Discipline

The Board has broad discretion to determine the suitable penalty to be imposed where cause for discipline is found to exist. The Board may discipline a physician, if found guilty of the charges, by any of the following methods: (1) suspending judgment, (2) placing the physician on probation, (3) suspending the physician's right to practice for any period not exceeding one year, (4) revoking the certificate and (or) (5) taking such other action in relation to discipline as the Board in its discretion may deem proper.

The question of the penalty to be imposed may be the single most important matter in the case for the physician. Evidence of mitigating circumstances may not be used to justify or excuse the unprofessional conduct but may be considered by the Board for the purpose of assessing the penalty. While mitigating circumstances will vary with the circumstances of each case, the following are examples which may apply in any given situation:

- The length of time the physician has practiced;
- The absence of any previous disciplinary action;
- The physician's reputation in the profession;
- Participation by the physician in civic and charitable activities;
- Good faith;
- Circumstances surrounding the act charged, such as the physician's attitude towards the act, and why it was done, and
- Efforts made by the physician to avoid a repetition of the offense.

Effective Date of Board's Decision

The effective date of the Board's decision, generally 30 days after the decision is delivered or mailed to the physician, is important to the physician for at least four reasons: (1) It informs the physician as to when the suspension or revocation of the physician's license commences. (2) It begins the running of the period in which judicial review may be instituted (30 days after the effective date of the decision). (3) It is the date when the Board loses power to reconsider or otherwise modify or change its decision or action. (4) It begins the running of the one-year period during which a physician whose license has been revoked or suspended may petition the Board for reinstatement or for reduction in penalty.

Judicial Review of the Board's Decision

Before resorting to the courts for relief, the physician must exhaust all available administrative remedies. This means that the physician must not only raise all relevant issues before the Board, but he or she must pursue the entire proceeding to a final decision on the merits. However, if an administrative remedy is not available, as, for example, where the Board erroneously denies the physician's subpoena request before a hearing commences, the doctrine of exhaustion of administrative remedies does not apply, and the physician may apply directly to the courts for relief.

In California, assuming a full presentation of the physician's case has been made at the administrative level and all available administrative remedies have been exhausted, a petition to review the Board's decision may be filed in the appropriate California Superior Court. The only issues which, by law, may be raised before the Superior Court are (1) whether the Board proceeded without or in excess of jurisdiction, (2) whether there was a fair trial and (3) whether there was any prejudicial abuse of discretion.

During judicial review of Board disciplinary proceedings, the Superior Court judge may weigh the evidence to resolve conflicting testimony in the process of determining whether the Board's findings are supported by the weight of the evidence. It is important to remember in this respect that ordinarily no evidence other than the administrative record may be introduced before the judge.

The propriety of the penalty imposed by the Board is a matter vested in its sole discretion, and

its decision may not be disturbed by the judge unless there has been a manifest abuse of discretion.

If the judge in the Superior Court rules against the physician, the physician may appeal to the District Court of Appeal and, possibly, thereafter, to the California Supreme Court.

What Is Unprofessional Conduct?

It is beyond the scope of this article to review in any depth the question of what conduct constitutes unprofessional conduct. However, the article would not be complete without some consideration being given to certain aspects of this subject, brief though it may be.

Under California law, unprofessional conduct includes, but is not limited to, the following:

- Gross negligence;
- Repeated similar negligent acts;
- Incompetence;
- Gross immorality;
- Commission of any act involving moral turpitude, dishonesty or corruption, and (or)
- Any action or conduct which would have warranted denial of the certificate.

While gross negligence has not been defined by statute, the courts have generally defined it as being the want of slight diligence, the entire failure to exercise care, the exercise of so slight a degree of care as to justify the belief that there was an indifference to the interests and welfare of the patient, or that want of care which would raise a presumption of a conscious indifference to the consequences. A single act constituting ordinary negligence may not constitute grounds for discipline; however, pursuant to a recent change in California law, a pattern of similar acts constituting ordinary negligence may well establish gross negligence within the meaning of the law.

Unprofessional conduct has also been defined to include (1) the conviction of a crime involving narcotics or dangerous drugs (a plea of nolo contendere is deemed to be a conviction for this purpose), (2) prescribing dangerous drugs without previous examination of the patient and (or) medical indication, (3) prescribing a narcotic for a person not under the physician's treatment for a disease or condition, (4) prescribing a narcotic to an addict or to a person representing himself as such, (5) deceptive or anonymous advertising of medical business, (6) certain advertising relating to sex matters, (7) excessive indulgence in alcoholic beverages and (or) (8) procuring an abortion, except in compliance with law. A plea of nolo contendere to a felony charge involving moral turpitude, whether misdemeanor or felony, also constitutes unprofessional conduct.

In addition, the use of alcoholic beverages to the extent or in such a manner as to be dangerous or injurious to a physician, or to any other person or to the public, constitutes unprofessional conduct. In many cases, such danger to the public can only be established upon a showing of repeated or habitual use of alcohol.

Conclusion

Considerable anguish may be avoided by a physician defending against disciplinary charges by anticipating the possibility that charges may be brought, distasteful though the thought may be, and preparing for it in a timely manner. Consequently, a physician should make it a part of his or her daily routine to prepare and maintain complete records about each patient to whom treatment is rendered. Names, addresses and telephone numbers of all persons who may be potential witnesses for the physician in any disciplinary action should be recorded, as well as the substance of their expected testimony. Similarly, while it is fresh in the physician's mind, all reasons for taking or not taking certain actions concerning the patient should be recorded. Many physicians undoubtedly do this routinely. Suffice it to say, those who do not, invite trouble by waiting until charges have been brought and *then* attempting to recreate from past recollection and sketchy files the reasons which (the physician believes) justify certain acts or failures to act. The failure to keep adequate records may be a costly mistake for the additional reason that several years may intervene between the date of the alleged unprofessional conduct and the initiation of Board proceedings. It is important to bear in mind in this regard that since disciplinary hearings are not civil actions within the meaning of the statute of limitations, there is accordingly no statute of limitations to bar the proceedings. Therefore, the importance of having detailed, factual information available to assist in the refreshing process cannot be overemphasized.

Finally, it is strongly urged that a physician accused of unprofessional conduct by the Board procure experienced and capable legal counsel to represent him or her during the Board proceedings, even though the law allows the physician to appear without counsel.

Refer to: Veith I: Hygeia by the Bay—A city of health (Medicine in American History). West J Med 127:442-449, Nov 1977

Hygeia by the Bay—A City of Health

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I

UNTIL RECENTLY, it was customary before a Chinese moved into a new residence or place of business to consult a specialist in geomancy who investigated the appropriateness of the new location for the prospective tenant or purchaser of the property. In Chinese terms, the question had to be answered whether the Fēng Shui, the "wind and water" conditions, were favorable for the new inhabitant. If an unfavorable constellation was discovered, the land or business purchase would have to be cancelled or renegotiated for another one that was propitious for all concerned.

Nothing as simple is at hand for the Western customer. Here psychology has to be applied; that is, the prospective customers must be convinced by other methods, more subtle—or less. One such method is a name for the real estate that stresses beauty, good climate, scenic excellence or even health. This angle of psychology in the sale of real estate can be traced all over the globe in such designations as Buenos Aires, Montevideo, Clearwater, Belair, Bellevue, Winter Haven, Garden City and all the various "Parks." Not necessarily is the air as fresh as touted, the water as clear, the mountains visible or the place lush with parks and gardens, but such is the fate of those who fall for propaganda.

Our attention, therefore, was drawn to the spelling "Hygeia" of the classical Greek word Hygieia when we saw 12 years ago that our new property in Tiburon on San Francisco Bay was listed as "Parcel 13, Lyford's Hygeia" on the assessor's map for the County of Marin, California. This listing contained two good omens: 13 had often been my family's lucky number; Hygieia, the goddess of health, was the daughter of Asklepios, the Greek god of medicine, who plays no small part in my profession as an historian of medicine.

Alas, as it turned out, we should rather have had a Fēng Shui taken first, because after a life of seemingly good health, serious illness struck me almost immediately upon moving into No. 13 Lyford's Hygeia. Perhaps the very oddity that the propitious designation of our property failed to live up to its promise made me curious about the background and history of its name and of its originator Lyford whose traces are encountered so frequently in and around the town of Tiburon.

Lyford was a physician, Benjamin Lyford, MD, who lived in the San Francisco Bay Area from 1866. He died at the then considerable age of 64.

The central portion of Dr. Lyford's property in Marin Country, Lyford's Hygeia, which he acquired through his wife's inheritance, is now generally referred to as old Tiburon, and indeed is quite beautifully located (Figure 1). As waters from springs ever trickle from its hillside, we can well understand that the 19th century doctor associated its natural beauty with the promise of good health. This was all the more logical, as the belief in refuges of nature organized for health and righteous living was widespread in the medical and inspirational literature of his and many previous centuries in history.[1]

II

Plato conceived his *Republic* as the model for an ideal society in sickness and in health. His design was taken up again in Saint Augustine's *City of God* which, as the name indicates, placed religious and moral principles above those of

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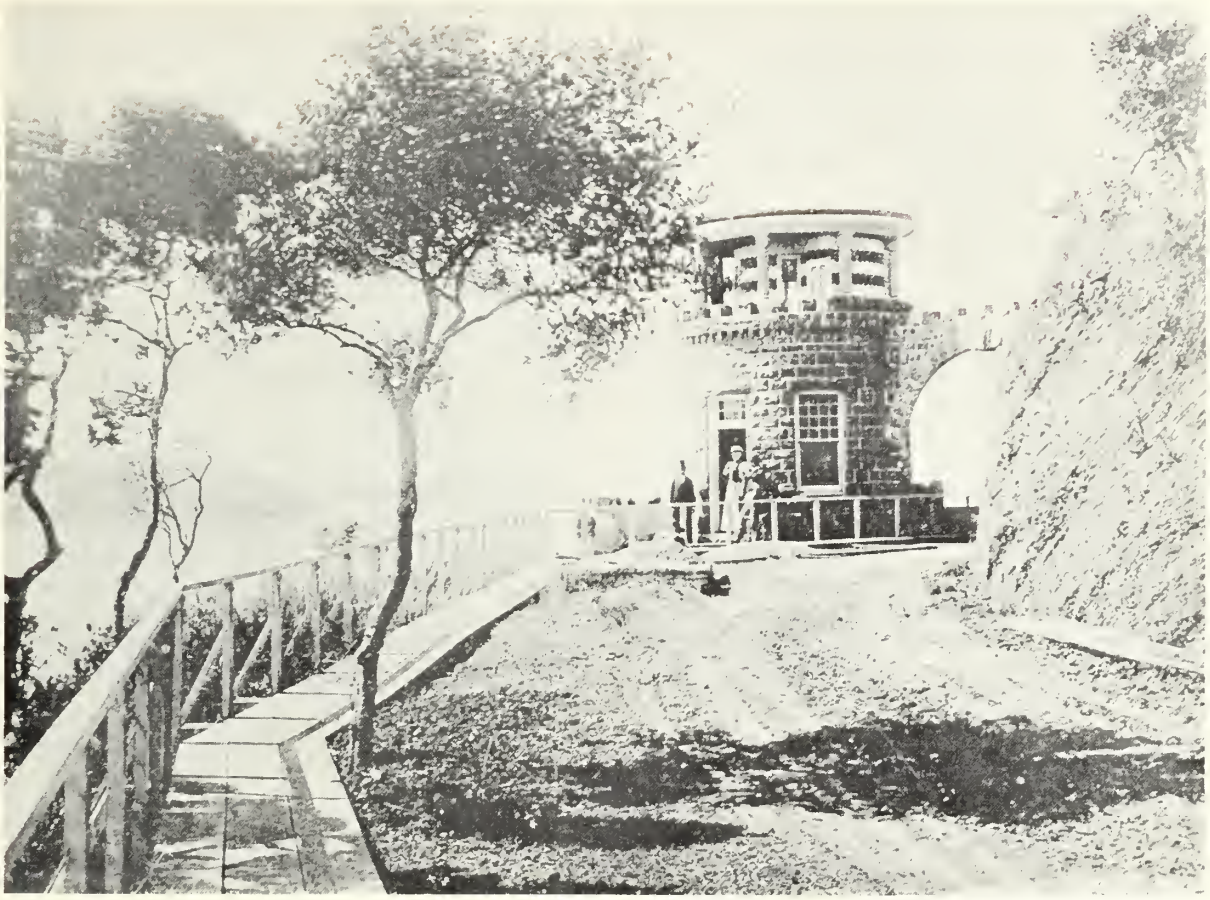

Figure 1.—Stone tower and entrance gate to Lyford's Hygeia. The stone tower is still in existence and the last remaining structure of the original Lyford's Hygeia.

physical health, earthly government and everyday living. In the 16th century, Sir Thomas More coined the term utopia (from the Greek ou, meaning none, and topos, meaning place) signifying nowhere or nonexistent, therefore implying a settlement that was too good to be true—a connotation that, in fact, it still maintains.

In the early 17th century, Sir Francis Bacon, a protegé of Elizabeth I and James I, created the phantasy of an imaginary island, the New Atlantis, which combined all the utopian advantages that had been envisaged by the previous writers.[2]

It is of special importance to note that the concept of the ideal community, regardless of its respective name, placed great emphasis on matters of the acquisition and maintenance of health, and at the same time on scholarship, science and learning. It has always been assumed that the maintenance of physical and psychological well-being depended upon the individual person's innate intelligence and its continued cultivation.

Most people in the western world encounter the essentially serious side of utopia first in the early years of their childhood through Jonathan Swift's famous tale of *Gulliver's Travels* that was first published in 1726. Far from simply being a tale for the amusement of children, this work is one of the best examples of utopian satire and fantasy and combines the ideas of most earlier utopian writers with much adjustment to contemporary medical and scientific knowledge. The story of *Gulliver's Travels* is a fictional, pseudo-autobiographical account of four voyages undertaken by a ship's surgeon, Captain Lemuel Gulliver. By making the protagonist of his story a medical man, Swift could follow the patterns of previous utopian voyages and make use of the biographies and travel reports of the many physicians who had journeyed to Asia in the employ of the English or Dutch East India Company. Moreover, the fictitious surgeon Gulliver quite logically made and recorded such medical and scientific observations that seemed worth noting to him.

It would go too far to follow Captain Gulliver's tour of inspection of the academy of science he found on his voyage, but it needs mentioning that even at the time of Jonathan Swift's writing, a single-minded preoccupation with the pursuit of science and learning was believed to produce that distinctly peculiar behavior and appearance which in our day has led to the designation of "egghead."

III

The utopias described so far, be they from Plato's, More's or Swift's fancy, resemble each other in several essential elements. They are all derived from the Atlantis legend and describe imaginary countries with ideal governments. In spite of the long time that had elapsed since the first utopian writings, it is by no means too much of an historical gap to consider these earlier literary utopias as possible sources of influence upon Doctor Lyford, the 19th century founder of "Lyford's Hygeia" on San Francisco Bay which was to be a community dedicated to healthful living.

Utopian thought and literature had by no means come to an end in 1516, when Sir Thomas More described his imaginary kingdom with its idealized Christian community and stress on health. In fact, so appealing was the concept of a community devoted to healthful living with equal rights for all, that beginning in the middle of the 17th century a number of settlers in this country joined to form utopian communities. We need only to remember the Dutch Mennonites who organized in Lewes, Delaware, and spread into numerous sister settlements throughout the continent.

The German pietist George Rapp gave rise to the founding of Harmony in Indiana, and Economy in Pennsylvania. Four of these settlements survived their founders, and some communal religious sects, among them the Hutterites, still flourish today. It is perhaps not surprising that other communities, such as the Shakers, in which celibacy was practiced, gradually passed into history, whereas the secular settlements that were founded by more worldly interests persisted, even including the famous settlement of Oneida that was established in New York in 1848. Founded by John Humphreys Noyes, the Oneidans practiced what was termed an extended family system, meaning a sharing of all husbands and wives. The problem of offspring was solved in a relatively easy fashion: The children resulting from this loose family system remained with their mothers until they could walk, after which time they were placed in communal nurseries.

In the course of time utopian family life was transformed from that of Thomas More's imaginary kingdom to the American commercial or farming communities that were bound by a quasi-religious belief or adherence to one charismatic leader. At the same time the meaning of the word "utopia" was extended and converted from the ideal and idealistic to the impractical, chimerical, visionary and even to the naively optimistic.

IV

Gradually also, the emphasis on the pursuit of science and healthful living receded from the tenets of the modern utopian writers, until we come to Dr. Benjamin Ward Richardson's *Hygeia, A City of Health,* which was published in 1876.[3] As Dr. Richardson, a noted medical author, and Fellow of the Royal Society and many other prestigious British organizations, was well known through his other publications in America also,* there is a distinct possibility, if not probability that his *Hygeia, A City of Health,* a widely read book of its day, caused Dr. Lyford to name his Tiburon property, "Lyford's Hygeia." In fact, the spelling of Hygeia, instead of the classical Greek Hygieia, may be a further indication that Lyford had derived his idea from Richardson.

Dr. Lyford could have learned much from Richardson, who had a complete grasp of the history of medicine as well as of the contemporary medical scene. Richardson's plan for Hygeia specified the design of the individual houses; the need for thorough ventilation in kitchens and bedrooms, the absolute necessity for privacy, insured by a certain amount of space between houses. Most important, perhaps, in the design for Hygeia, and adapted by Dr. Lyford to his property, was an innovative sewer system, under the direction and supervision of a "sanitary office." There was also a remarkably efficient design for "water closets" in the model city.

> The water-closets in the houses were to be situated on the middle and basement floors. A continuous water-supply flushes them without danger of contaminating the drinking-water with gases emanating from the closet; which was a danger so imminent in the prevalent method of constructing cisterns, which supply drinking as well as flushing water.

*Benjamin Ward Richardson's most widely known book was: *Diseases of Modern Life.* New York, D. Appleton and Company, 1876.

Figure 2.—Dr. Benjamin Lyford shortly after his arrival in San Francisco and the opening of his medical practice.

A further rule in Richardson's model city, subsequently followed by Dr. Lyford, was the prohibition of the sale of tobacco and alcoholic beverages. Richardson wished to make his Hygeia a "total abstainers' town."

Lyford was somewhat more realistic in anticipating his fellow countrymen's reaction to such prohibition. He knew that he might not find enough settlers for his Tiburon Hygeia if he insisted on total abstinence. Hence he stipulated only that the contract for the sale of property contain a legally binding clause against the sale of tobacco and alcohol on the premises; gambling and dancing were also forbidden on a community-wide scale. The contracts, however, of which a few samples have been preserved made explicit allowance for the use of tobacco and alcohol within the private confines of the individual families in which setting also an occasional game of cards and dice was permitted.

Because of its relatively small size, Lyford's Hygeia could not possibly contain any of the model hospitals that had crowded the imagination of Benjamin Ward Richardson. Nevertheless, it will be worthwhile to describe Richardson's concept of the ideal hospital in contrast to those in existence in his day. He spoke of abandoning the "old idea of warehousing diseases on the largest possible scale, and of making it the boast of an institution that it contain so many hundred beds." Furthermore, abandoned by Richardson was the idea of "building an institution so that it shall stand for centuries, like a Norman castle." Richardson also considered as absurd the practice of "building hospitals for the treatment of special organs of the body, as if the different organs could walk out of the body and present themselves for treatment."*

Even if Dr. Lyford, who imitated Richardson's *Hygeia, A City of Health* in so many respects, was unable to follow his suggestions for the construction and planning of hospitals, it does repay one to study these thoughts, as even today many hospitals left over from the quasi-Norman castle period are far from the practicality and efficiency of the hospitals envisaged by Richardson. Of special pertinence to all times, even to the present, was the provision that in medical practice "the order that prevails was to be so effective that a person, who is punctual to time, never has to wait."

V

We cannot conclude our reflections on the origin and purpose of Lyford's Hygeia without another glance at the personality and background of its founder, Dr. Benjamin F. Lyford, who was said to have carried a busy and highly successful medical practice on 400 Kearny Street in San Francisco from the year 1866 (Figure 2).

Dr. Lyford was born in 1841 in Vermont not far from the Canadian border. He was said to have received his elementary education in Canada. As to the nature of his medical studies, and of the origins of his degree, little precise information is available. Professor J. H. Guinn, a California historian, agreed with the then prevalent rhapsodic assessment of Dr. Lyford's medical skills in eulogizing his research and studies exuberantly:[4]

> Naturally a profound student, as his means increased he devoted more and more time to the pursuit of his scientific investigations, finally retiring permanently from general practice in 1876. Since that year he has contributed to the world of medicine and surgery a vast amount of valuable information, all the direct result of his individual research and exhaustive study.

Furthermore, according to Professor Guinn, Dr. Lyford was not only a philanthropist, he was

*This and all previous quotations from Richardson's life of health are taken from *Hygeia, A City of Health* by Benjamin Ward Richardson.[3]

"a scientist and an inventor and honored among the noted men who have devoted their lives to medicine and surgery." The scientific discovery for which Lyford is said to have been widely celebrated was a new method of embalming, by means of which the body may be preserved indefinitely in a most lifelike state. This method reportedly caused a considerable stir in medical circles, but they were unable to reproduce Lyford's accomplishment. Actually, this was not surprising, as Lyford, in applying for a patent for his invention, had not made known his secret for the entire formula.

VI

This breach of medical ethics in withholding information from his colleagues and exploiting it solely for his own pecuniary benefit may have been a result of his inadequate medical schooling, during which he was unable in his own formative years to model himself after any ideal medical figure. Yet, Guinn rhapsodized about Lyford having pursued his medical studies in New York City; "being graduated with honors from one of the best medical colleges." Instead, however, we know from Lyford's own testimony during a murder trial in which he served as expert witness on behalf of the accused, that he had graduated from a totally insignificant proprietary medical school, the Philadelphia University, where he had been enrolled for a period of six or seven months.[5]

This brief and haphazard period of medical schooling which appears so completely inadequate by today's exacting standards of medical education, was not in the least extraordinary in 19th century America. Until the second decade of our century, medical education was dispensed in a great number of proprietary medical schools which had sprung up all over the country. The prospective doctors attended these schools after a period of apprenticeship to a mature and experienced physician. The curriculum of the proprietary medical schools usually consisted of one semester's instruction in both the basic and the clinical sciences, and possibly another semester of repetition of exactly the same instruction. Only when the famous Flexner report on medical education had exerted its impact, and a vast number of unsupervised proprietary medical schools had gone out of business, could the remaining academic schools of medicine proceed to the thorough training of modern physicians. Regardless of the brevity of his medical education, Lyford

Figure 3.—Hilarita Reed Lyford in the early years of her married life.

was entirely justified in calling himself Dr. Lyford, as the Philadelphia University had actually conferred the MD degree upon him.

Lyford's military record in the Civil War had a less than glorious ending. As Assistant Surgeon of a "Colored Infantry Regiment," Lyford was accused of having visited on December 20th, 1865, a New Orleans house of ill fame in uniform. This infraction of army rules caused him to be charged with conduct unbecoming to an officer and a gentleman. A few weeks later, early in 1866, Lyford cleared himself of these charges by convincing the Adjutant General that his visit to that house had been in pursuit of his military duty in order to find a steamboat clerk, and that, furthermore, not once in his life had he patronized a house of that kind, and that he held "such habits in supreme contempt."

The Adjutant General let himself be convinced that Lyford's visit was actually made on business and took no action. Nevertheless, approximately one month after that incident, on February 6, 1866, Lyford was mustered out of the Army.

Figure 4.—Dr. Benjamin Lyford's Eagle Dairy on Strawberry Point, Marin County, California. Visible in the center is the private residence of Dr. and Mrs. Lyford.

VII

It was then that he came to San Francisco and opened his medical office at 400 Kearny Street. Although he soon built up a busy practice, he ordinarily would have been far from able to acquire the large tract of land in Marin County now known as Lyford's Cove or Lyford's Hygeia, and from engaging in his time-consuming researches on embalming and the improved sewer system. Such pursuit of extraneous activities obviously was based upon the change in his personal fortunes through the person of his patient, Hilarita Reed (Figure 3), the lovely young daughter of the late John Thomas Reed. Reed of Ireland had been the owner of the 8,000-acre Rancho Corte Madera del Presidio in Marin County, an enormous tract of land granted to him in 1834 by the Mexican Government. Dr. Lyford not only eagerly gave advice to Hilarita and her siblings on the utilization of their large land holdings, but he also married Hilarita in 1872. Although his wife was now a co-owner of the vast Rancho Corte Madera del Presidio in Marin County, the Lyfords continued to live in San Francisco, to avoid the strain of commuting and the upheaval on the ranch that was caused by rebuilding and landscaping.

It was during these years of residence in San Francisco that Dr. Lyford made a name for himself in connection with his invention of the abovementioned embalming process. So impressive was his skill as an embalmer that a San Francisco newspaper[7] on November 26, 1870, made the following report about the body of Mrs. Concepcion Ward of Alameda County, which had been embalmed two and a half years before:

> Since that time the body has remained in a casket, exposed to the air in an open room, but to this day no change in its condition has taken place. The entire body is solid as a petrefaction. The fullness and color of the flesh are remarkably preserved, and the whole appearance is almost startingly life-like.

VIII

As Dr. Lyford's endeavors were not concentrated on his skill as an embalmer, and he was no longer economically dependent upon the income from treating patients, he decided to retire

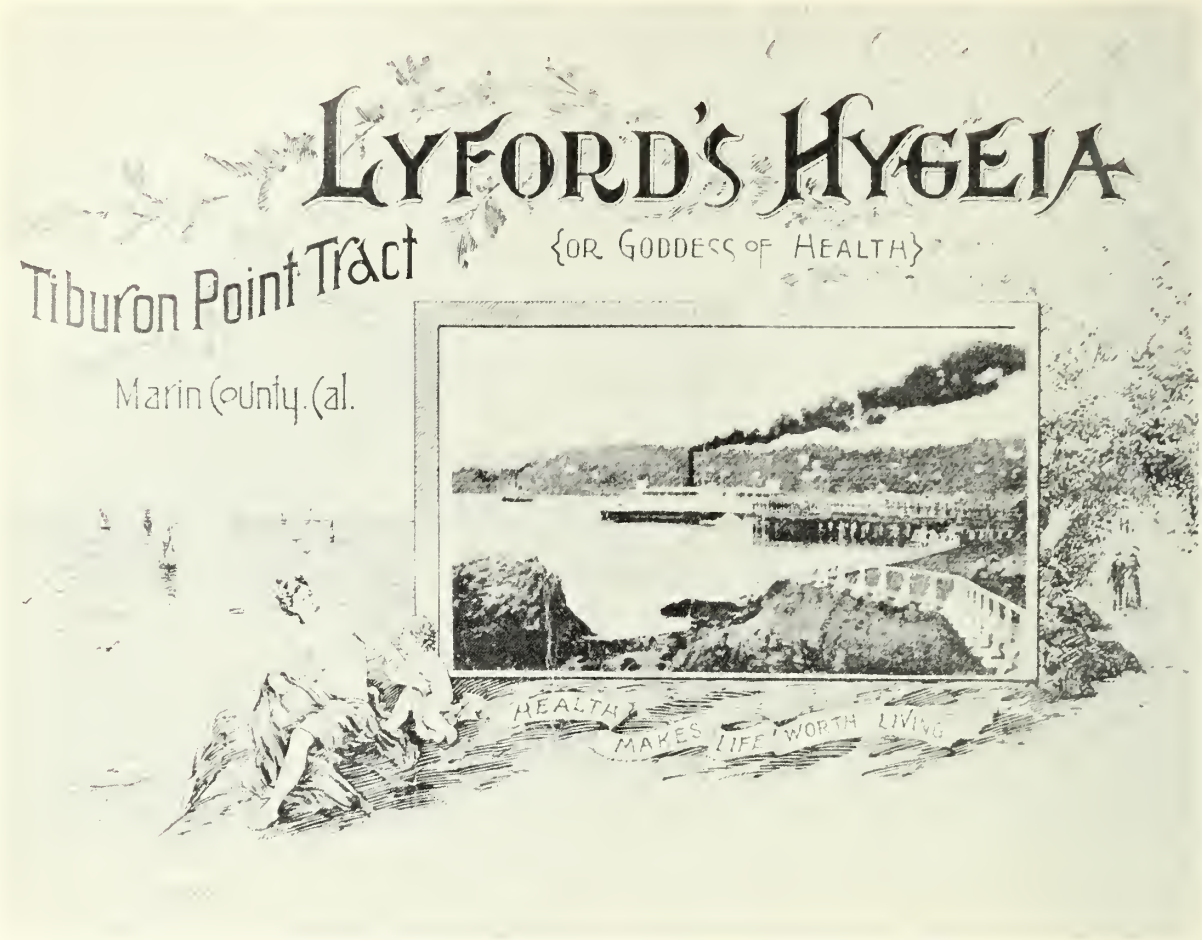

Figure 5.—Cover of the sales brochure advertising Lyford's Hygeia.

from active practice. In preparation for their retirement to their property in rural Marin County, Dr. and Mrs. Lyford built a house of Victorian Gothic design with a three-story tower. This unusual house (Figure 4) was built with extraordinary cost and care. The delivery of the exotic building materials and the personal access to the Lyford House were facilitated by a new railroad line of the North Pacific Coast Railroad that connected the Reed Ranch with San Rafael. The railroad had been built by work gangs of Chinese coolies during the last years of the Lyfords' residence in San Francisco, and it terminated directly behind their new house on the Strawberry peninsula at what was once known to be Lyford Station.

With his removal to Marin County, Dr. Lyford continued to make a name for himself with his successful dairy farm and business, as well as with the pursuit of his embalming feats and the installation of his modern sewage system in Lyford's Hygeia, his small city of health.

IX

After the study of Dr. Lyford's medical and scientific efforts, it is disappointing to realize that much of it was pure pretension, and that his yearnings for the pursuit of Lyford's Hygeia actually was a well-conceived plan for a successful real estate venture. Instead of using his own presumably scientific prose to make known the availability of building sites in Lyford's Hygeia, Dr. Lyford employed a realtor and public relations expert, Jared C. Hoag, who composed a sales prospectus (Figure 5) for *Lyford's Hygeia (Goddess of Health) and Tiburon Point Tract.* (For the loan of the last extant copy of this extraordinary document, as well as for many of the illustrations, I am indebted to the Belvedere-Tiburon Landmark Society, and especially to the kindness of Mrs. Louise Teather of Tiburon who made available to me many of the documents related to this story.)

Mr. Hoag's advertisement of Lyford's Hygeia

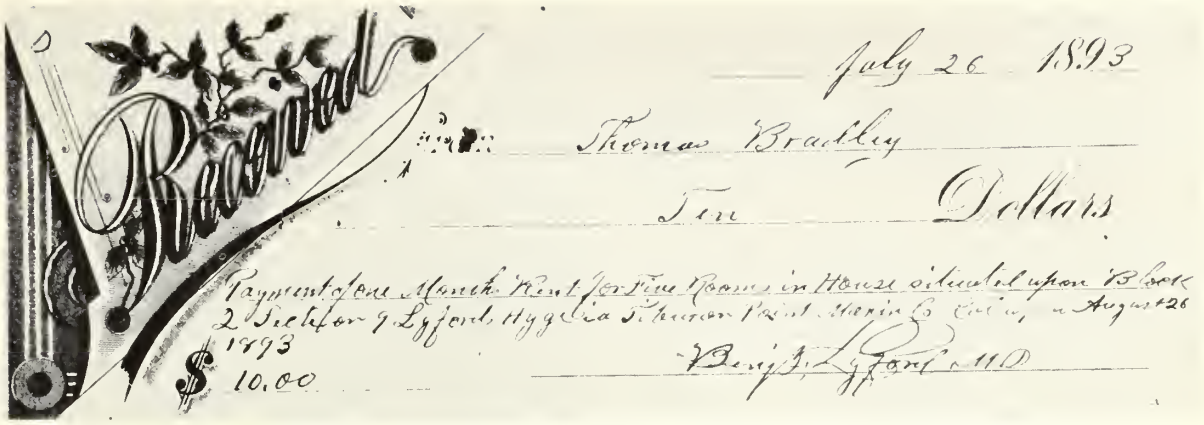
Received July 26 1893
Thomas Bradley
Ten Dollars
Payment for one Month's Rent for Five Rooms in House situated upon Block 2 Section 9 Lyford's Hygeia Tiburon Point Marin Co Cal, August 26 1893
$ 10.00
Benj. F. Lyford M.D.

Figure 6.—Receipt for $10 for one month's rent of a five-room house in Lyford's Hygeia.

told the sad story of lost health which can be restored by science and money, that is, by settling at Lyford's Hygeia. Not a second did he hesitate to compare Tiburon with Nice, Cannes, and all the other health resorts of the South of France; the resorts of Italy, including Sardinia and Sicily; Bermuda; Malta; Florida, and all the other watering places in Europe and America.

In apparent anticipation of the concerns of the environmentalists over the deterioration of our natural resources, Mr. Hoag wrote ecstatically:

> Of this marvelous spot, which even now events are shaping to become the most far-famed health resort the world has known, of its matchless combination of location, climate, water facilities, freedom from fogs, noxious vapors, and in a word, total immunity from all those elements which retard growth and ultimately destroy life, much has been written, but its true story and the story of the almost supernatural foresight which seems to have guided him who has been foremost in bringing its advantages, its unequaled climatic conditions before the world is yet to be told.

It is scarcely surprising that Mr. Hoag's prospects of Tiburon Point Tract concluded with an essay on the Eagle Dairy, making it appear as though Lyford's concern in this enterprise was solely for the benefit to mankind and not the monetary reward it might bring.

Once Lyford's Hygeia had become a fully operative residential section of Tiburon (an 1893 rental receipt is shown in Figure 6), and the Eagle Dairy a lucrative venture, Dr. Lyford seems to have lost interest in the further pursuit of his plans for that little city of health, and led his own quiet life on Strawberry Point. The extraordinary house which he had built for himself and his wife Hilarita has, since his death in 1905, been relocated several times within the confines of Marin County and now serves as a headquarters in a sanctuary of the Audubon Society. Perhaps Dr. Lyford is taking posthumous pleasure in the knowledge that his erstwhile property is dedicated to the preservation of health and life—even if it is only of the animals of the San Francisco Bay Area.

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Information

Refer to: Boyce-Smith G, Zier B, Deller JJ: Deficiencies in the training of internists: Results of a survey (Information). West J Med 127:450-452, Nov 1977

Deficiencies in the Training of Internists

Results of a Survey

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DURING THE PAST ten years medical education for physicians has undergone a dramatic revision. The trend has been a decline in medical and surgical subspecialty training, and an increase in emphasis on preparing physicians for careers in primary care. Evidence for this development is found in the growth of new housestaff training programs in primary care such as the residency programs of Massachusetts General Hospital,[1] Emory University[2] and University of California, San Francisco,[3] and the Social Medicine Residency at the Montefiore Hospital in New York.[4] Debates published in the editorial pages of prestigious journals[5-7] have centered on which department (medicine versus family practice) or what site (rural versus urban) should foster this training. The National Academy of Sciences has proposed a policy decision to limit the number of subspecialists being trained and to concentrate on developing more primary care practitioners.[8]

In light of this trend we felt it would be useful to survey a sample of physicians who have completed their training in internal medicine and are now established in private practice. The purpose of this survey was to elucidate the various elements of internists' practices and to ascertain whether or not these physicians thought there were deficiencies in their training that would reflect a need for change in postgraduate medical education of physicians entering primary care practice.

The following key questions were posed:

- In your practice of internal medicine do you see patients with problems in interdisciplinary areas not included in traditional housestaff training in internal medicine? If yes, what percentage of such patients must be referred to appropriate subspecialists or specialists?
- Would additional training in interdisciplinary areas have helped you to deal more effectively with your patients' problems?
- Would more postgraduate courses in the common problems of the interdisciplinary areas be appropriate for general internists and primary care internists? If yes, in which specific areas should the postgraduate courses be offered?

Methods

At an American College of Physicians postgraduate course (Internal Medicines and the Practice of Internal Medicine, January 20 through 23, 1976, at Letterman Army Medical Center, San Francisco, California), physicians who were in the active practice of internal medicine (general or subspecialty) or other areas (such as pediatrics or family practice) were asked to fill out questionnaires. The sample population was composed of 107 physicians* who are in various settings throughout the United States. Basic data were gathered regarding age, years in practice, practice setting, percent of practice doing general internal medicine and percent of time treating other problems. The physicians were asked to give answers to the key questions listed above. The results were tabulated, and the responses were grouped in two large categories: physicians with (1) less than ten years of practice and (2) more than ten years of practice.

Results

Of the 107 physicians in the sample, 99 (92.5 percent) were practicing general internal medicine or one of its subspecialties (Table 1). A total of 74 general internists indicated that more than three quarters of their practice time was spent doing general internal medicine, while of the 25 subspecialists, 80 percent indicated that

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The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army, Department of Defense, or the professional affiliations of the authors.

Reprint requests to: Gifford Boyce-Smith, MD, Ambulatory Care Center Buildings, A-405, University of California Medical Center, San Francisco CA 94143.

*There were a total of 307 registrants, but approximately 100 were housestaff members or physicians in fields other than internal medicine. The sample represents approximately 50 percent of the other participants.

they spent more than half of their time in the practice of general internal medicine.

More than a third of all the patients seen by these physicians had medical problems that prompted referral to other specialists or subspecialists by 30 percent of the younger group of physicians and 40 percent of the older group. The primary reason given for referral, according to this sample, was lack of confidence in treating these problems. Table 2 summarizes the percent of patients referred to specialists or subspecialists. Table 3 tabulates responses of the physicians about their preferences for interdisciplinary training.

TABLE 1.—*Practice Characteristics of the 107 Physicians Sampled*

	Physician Age Range	
	28-52 Years *<10 Years in Practice*	*35-60 Years* *>10 Years in Practice*
Type of Physician		
General Internists	39	35
Medical Subspecialists	17	8
Pediatricians	1	0
Family Practitioners	3	0
Occupational Medicine	0	2
Other	0	2
Total	60	47

TABLE 2.—*Percent of Patients Referred to Specialists or Subspecialists by the Internists**

	Years in Practice	
Referral Rate (percent) Patients	*<10 Years (percent)*	*>10 Years (percent)*
Less than 25	49	50
Approximately 35	21	10
Approximately 50	14	17
Approximately 65	5	0
66 to 75	11	23

*93 of 107 physicians in sample responded.

TABLE 3.—*Internists' Preferences for Interdisciplinary Training*

		Time in Practice	
		<10 Years (percent)	*>10 Years (percent)*
Would additional training in interdisciplinary areas help you to deal more effectively with your patients' problems?	Yes	75	65
	No	28	35
Are you interested in more postgraduate courses in the interdisciplinary areas?	Yes	90	65
	No	10	35
In which specific areas should postgraduate courses be structured?			
Dermatology		67	100
Neurology		100	62
Psychiatry		89	33
Gynecology		78	33
Genitourology		11	21
Otorhinolaryngology		33	37
Orthopedics		89	42
Ophthalmology		0	21

Discussion

On May 2, 1892, while addressing the fourth annual meeting of the Pediatric Society held in Boston, William Osler said, "No more dangerous members of our profession exist than those born into it, so to speak, as specialists."[9]

Specialization over the past 30 years has been necessary to keep pace with the rapid advances in medical knowledge and technology. However, specialization has been accentuated to the point where general internists with office practice no longer feel confident in taking care of many of the common ills of their patients. This situation epitomizes Osler's statement.

Furthermore, most current residency programs in internal medicine, especially at major university centers, have focused almost exclusively on the inpatient and his more complex problems. This same trend carries over to the majority of postgraduate courses which rarely extend beyond the traditional confines of internal medicine. Thus the needs of the physician entering or actively engaged in the practice of general internal medicine are not being met.

From this survey, several things are evident: (1) the majority of internists practice "general medicine"; (2) the majority of internists in practice feel that they would benefit from additional training in some of the interdisciplinary fields, and (3) a large number of patients are referred to other specialists or subspecialists for problems which could be handled by a more broadly trained general internist.

Dermatology and neurology are the interdisciplinary specialties that practicing internists feel should be given greater emphasis during residency training. Younger internists also have strong preference for more office psychiatry, nonoperative orthopedics and gynecology. Both young and older physicians show a similar interest in more exposure to nonoperative otorhinolaryngology.

Our data come from physicians already motivated to continue their education. We cannot therefore use these results to answer *why* there seems to be an increasing interest in interdisci-

plinary problems among general internists in practice. There was no significant difference in the referral pattern or percent interested in more interdisciplinary training between the older and younger physicians in our survey. We can say, therefore, that it is not a matter of the young being more receptive or the older having already taught themselves these skills.

This information should not be construed to suggest a radical departure from the current high standards of excellence in training in the classic discipline of internal medicine; these remain the foundation of our specialty. We should, however, be able to accommodate a better balance in our training experience so as not to neglect many of the problems seen in the office practice of internal medicine.

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Surgical Treatment of Vertigo

THE WHOLE BUSINESS of balance can be made analogous to a computer system. A computer, as we all know, has an input, a central analyzer and an output. As far as the vestibular system is concerned, the input consists primarily of information from the labyrinth. Semicircular canals signal changes in angular acceleration, the utricle signals linear changes in regard to gravity, such as nodding and bending movements; so there is a constant electrical output from the semicircular canals and from the utricle at rest which changes as the result of stimulation. When the activity on one side increases, there is a matching decrease of activity on the other side, and this information is, with the passage of time from the moment of birth up until the age of 12, gradually assimilated and made into something that is meaningful to the brain stem. So from about that time onward, if all goes well, we can perform most tests of balance and perform most movements in the expected fashion. The other inputs in the "computer" are derived from the musculoskeletal system and, most important, from the sensors of the spinal column, the large joints and the muscles, and particularly from the head and neck region. And finally, of course, there is the input from the retina, the visual input. Now all of this information is brought together in the brain stem and analyzed in the light of past experience; the output is then distributed to the sensory cortex to tell us where we are in space, to the motor cortex to instruct the muscles of the limbs to contract and relax appropriately, to the eye nuclei so that the last field of gaze is maintained. The eye maintains the last field of gaze so that when I turn my head I know that what I'm seeing is not turning with me. And finally, information is sent to the alimentary canal so that if I were at this moment to stand on my head, you wouldn't have a view of my breakfast. This is how the system works normally.

—GORDON D. L. SMYTH, MD, *Belfast*

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BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

OPHTHALMIC PLASTIC SURGERY—Fifth Edition—Sidney A. Fox, MS(Ophth), MD, MED SCI D (Hon), Quondam Clinical Professor of Ophthalmology, New York University School of Medicine; Visiting Ophthalmologist, Bellevue Hospital; Consultant Ophthalmologist, Bronx VA Hospital, Goldwater Memorial Hospital, Hospital for Joint Diseases and Medical Center, St. Vincent's Hospital, and Cabrini Medical Center. Grune & Stratton, Inc., Medical and Scientific Publishers, 111 Fifth Avenue, New York City (10003), 1976. 666 pages, $39.50.

This is a greatly expanded version of the well-known text on ophthalmic plastic surgery by Dr. Sidney Fox. This increasingly important subspecialty is covered organizationally in this text by a series of chapters dealing with general principles, which is followed by extensive and detailed discussions of the management of specific lesions.

A discussion of lid, orbital and adnexal anatomy is followed by a welcome chapter written by Allan Friedman and Paul Henkind on the clinical and pathological features of eyelid and conjuntival tumors. Additional general topics are covered in chapters on the technical details of patient preparation, instrumentation, anesthesia, sutures, pegs, molds and postoperative care. General principles of grafting are discussed extensively, and certain basic techniques in ophthalmic plastic surgery are given special discussion in a separate chapter.

Details of the management of specific lesions are then covered in a systematic chapter-by-chapter classification which includes among others, discussions of lid lesions (extramarginal, large and small marginal lesions), medial and lateral cantal-lesions, major upper and lower lid reconstructions, ectropion, entropion, ptosis, cosmetic surgery, conjuntival plastic surgery, congenital and acquired anomalies, socket and orbit repairs, enucleation, lacrimal system problems and some miscellaneous topics such as tattooing, trauma, radiation (written by Joseph Newhall, M.D.) and hair-bearing grafts.

Dr. Fox's writing is among the most lucid in the ophthalmic literature, and he is one of the few authors who can describe a procedure so accurately that it is generally possible to do it following a careful reading of the description, even if the procedure has never been seen by the surgeon. While this is not a recommendation for such an approach, it is a tribute to the clarity of style which is displayed in this book. On the other hand, one might have wished for more revision of many of the drawings to bring them into more current and diagrammatic style. While numerous acceptable and very useful illustrations are naturally included, there is an occasional sense that more step-by-step diagrams would be helpful, especially to inexperienced readers. In addition, the mixture of various artistic styles is somewhat disconcerting and less easy to follow than consistent styles might be.

Any text is certain to project the author's particular bias, and ophthalmic plastic surgery has its share of controversy and varied approaches and techniques. The author tends to recognize these differences and to refer to them in print, and this not only enlivens the prose but keeps the reader apprised of the availability of alternative approaches. There will, however, be surgeons who specialize in this field who will disagree with some of the suggestions of the book and who would probably prefer that alternative approaches be given more complete treatment. Nevertheless, especially for students or for ophthalmologists not specializing in this particular field, this book is an outstanding and eminently readable reference. It should continue to occupy an important place in any ophthalmic library, and it would clearly be a worthwhile investment for residents or ophthalmologists beginning to develop their interest in ophthalmic plastic surgery.

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* * *

DRUG TREATMENT—Principles and Practice of Clinical Pharmacology and Therapeutics—Edited by Graeme S. Avery, Editor-in-Chief: Australasian Drug Information Services Pty Ltd, Sydney & Auckland; Editor: Drugs, Clinical Pharmacokinetics. Publishing Sciences Group Inc., 162 Great Rd., Acton, MA (01720), 1976. 1048 pages, $25.00.

The basic theme of this book is the selection and use of drugs within a disease-oriented context. This conception has resulted in a different format than most pharmacology texts. Dr. G. S. Avery, Editor, hopes it will bridge the gap between textbooks emphasizing diagnosis and pathophysiology of disease to therapeutics.

The book is organized into three sections: (1) Clinical Pharmacology—Describes the clinical significance and use of basic pharmacokinetics and bioavailability factors in arriving at individual drug therapy, the cornerstone of clinical pharmacology. In addition there are chapters on the unique problems of prescribing for pediatric and geriatric patients, emphasizing the particular susceptibility of the elderly to adverse drug reactions and unique problems associated with self-medication in old age. The section ends with several chapters on adverse drug reactions and drug-drug interactions. (2) Therapeutics—Drug therapies of general categories of disease are considered in this section; for example, skin, endocrine, cardiovascular and respiratory diseases. In general, consideration is given not only to the therapeutics in various disease states but also to what effects the disease state may have on the effect of the drug, its metabolism, distribution and excretion. A balance is attempted between trying to explain how and why a drug works and treatment. At times this seems artificial. (3) Appendices—This is a wealth of information collected together in one place that practicing physicians or students would be hard pressed to find easily on their own; particularly Appendix A, where items such as plasma half-life, volume of distribution protein binding and the like are tabulated for many commonly used drugs.

Drug Treatment is a compilation by many internationally recognized experts in clinical pharmacology; a small number of the drugs suggested are not available in the United States. The book is highly structured, well organized, and contains many subheadings in each chapter. Each chapter begins with a synopsis of important principles and ends with many recent references.

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in memoriam

Benninghoven, Carl Donald, San Mateo. Died September 18, 1977, aged 75. Graduate of the University of California Medical School, Berkeley-San Francisco, 1930. Licensed in California in 1930. Dr. Benninghoven was a retired member of the San Mateo County Medical Society.

Cameron, Markley Connell, jr., Beverly Hills. Died July 28, 1977 in Santa Monica of cardiac arrest following lengthy illness, aged 75. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1927. Licensed in California in 1932. Dr. Cameron was a retired member of the Los Angeles County Medical Association.

Cooper, Ward, Palo Alto. Died September 25, 1977 in Palo Alto, aged 92. Gaduate of the University of Illinois College of Medicine, Chicago, 1916. Licensed in California in 1922. Dr. Cooper was a retired member of the Santa Clara County Medical Society.

Curtis, Mark S., Bakersfield. Died September 3, 1977 in Bakersfield, aged 62. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1939. Licensed in California in 1946. Dr. Curtis was a member of the Kern County Medical Society.

Elvin, John Henry, Pismo Beach. Died September 26, 1977 in San Luis Obispo, aged 89. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1930. Licensed in California in 1930. Dr. Elvin was a retired member of the San Luis Obispo County Medical Society.

Frantzich, Otto A., Oceanside. Died September 9, 1977, aged 58. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1952. Licensed in California in 1953. MD degree from California College of Medicine, 1962. Dr. Frantzich was a member of the Los Angeles County Medical Association.

Frederick, John David, Maywood. Died August 31, 1977 of injuries received in a plane crash, aged 49. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1955. Licensed in California in 1956. Dr. Frederick was a member of the Los Angeles County Medical Association.

Goldenberg, Julius L., Palm Springs. Died August 12, 1977 of heat disease, aged 70. Graduate of the University of Minnesota Medical School, Minneapolis, 1929. Licensed in California in 1934. Dr. Goldenberg was a retired member of the Los Angeles County Medical Association.

Graveline, Edwin, Fresno. Died September 22, 1977 of heart disease, aged 59. Graduate of St. Louis University School of Medicine, 1944. Licensed in California in 1946. Dr. Graveline was a member of the Fresno-Madera Medical Society.

Hepplewhite, James G., Chico. Died January 25, 1977 of emphysema, aged 83. Graduate of the University of California Medical School, Berkeley-San Francisco, 1923. Licensed in California in 1924. Dr. Hepplewhite was a retired member of the Butte-Glenn Medical Society.

Killen, Richard Beaman, Berkeley. Died September 2, 1977 in Oakland, aged 43. Graduate of the George Washington University School of Medicine, Washington, DC, 1959. Licensed in California in 1960. Dr. Killen was a member of the Alameda-Contra Costa Medical Association.

Rosenthal, Ludwig T., Beverly Hills. Died October 17, 1976 in Los Angeles of metastatic adenocarcinoma of the colon, aged 64. Graduate of Deutsche Universität Medizinsche Fakultät, Prague, 1936. Licensed in California in 1946. Dr. Rosenthal was a member of the Los Angeles County Medical Association.

Rubell, Irwin, Los Angeles. Died August 28, 1977 of heart disease, aged 82. Graduate of the University of Illinois College of Medicine, Chicago, 1922. Licensed in California in 1943. Dr. Rubell was a retired member of the Los Angeles County Medical Association.

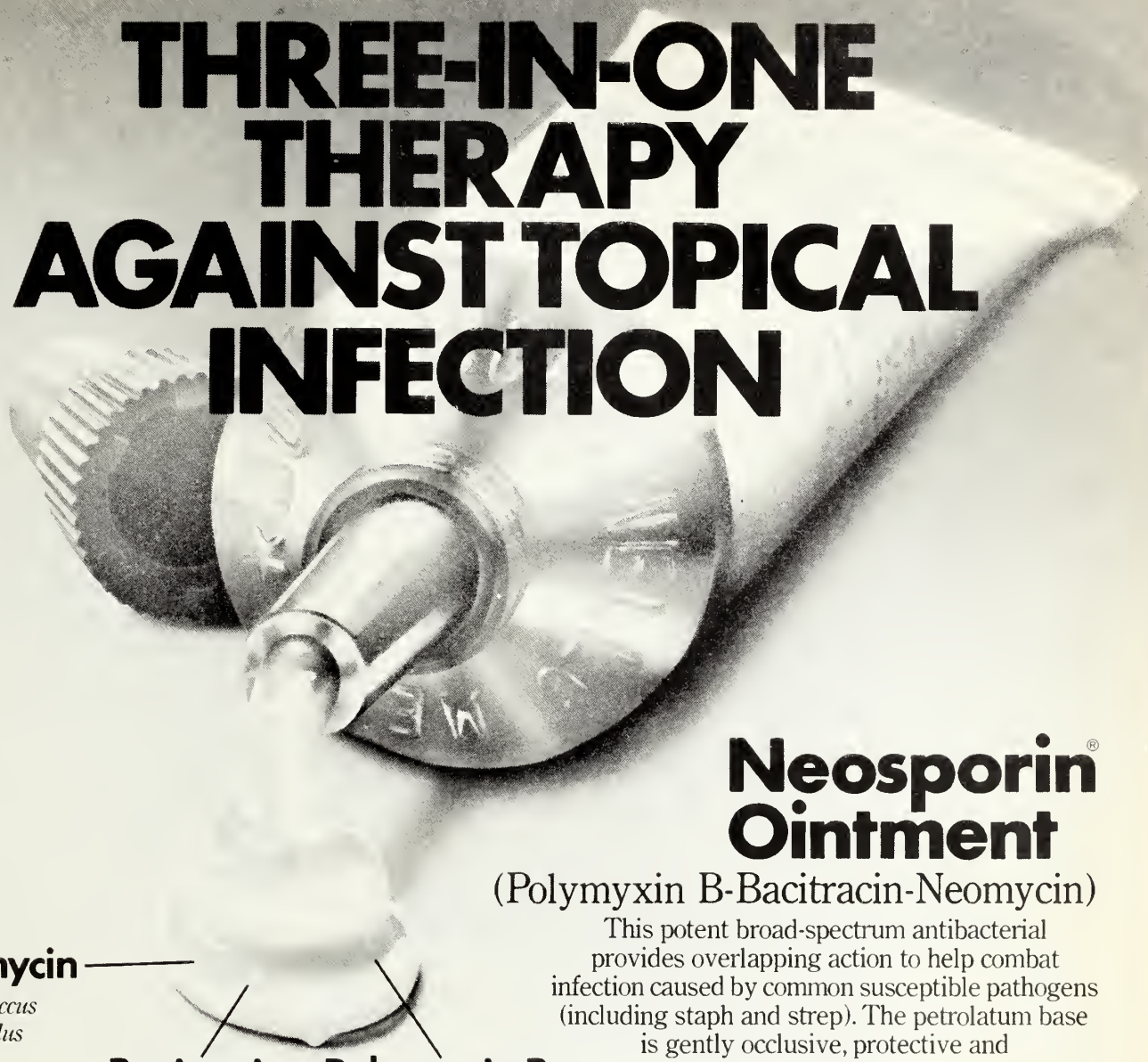
Strom, Gilbert Harold, Pico Rivera. Died April 29, 1977 in Downey of pulmonary embolism, aged 49. Graduate of Kansas City College of Osteopathy and Surgery, Kansas City, Missouri, 1960. Licensed in California in 1961. MD degree from California College of Medicine, 1962. Dr. Strom was a member of the Los Angeles County Medical Association.

Tarr, Agnes DeLawder, Taft. Died September 10, 1977 in Bakersfield, aged 69. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1937. Licensed in California in 1938. Dr. Tarr was a retired member of the Kern County Medical Society.

Thompson, James H., San Francisco. Died September 25, 1977, aged 63. Graduate of Harvard Medical School, Boston, 1940. Licensed in California in 1940. Dr. Thompson was a member of the San Francisco Medical Society.

Treweek, David N., Los Angeles. Died July 28, 1977 in La Jolla of carcinoma of the pancreas, aged 73. Graduate of Northwestern University Medical School, Chicago, 1930. Licensed in California in 1932. Dr. Treweek was a retired member of the Los Angeles County Medical Association.

THREE-IN-ONE THERAPY AGAINST TOPICAL INFECTION



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Bacitracin

Staphylococcus
Corynebacterium
Streptococcus
Pneumococcus

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WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

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PHYSICIANS WANTED

CALIFORNIA, Santa Clara County: Experienced, career-oriented emergency physicians wanted to join well established group. Fee-for-service compensation. Position available immediately. Please direct inquiries with curriculum vitae to Associated Emergency Physicians, Inc., 1530 The Alameda, No. 28, San Jose, CA 95126 or phone: (408) 956-5900.

THE TRUST TERRITORY of the Pacific Islands has openings for Internists. These are two-year assignments with housing and family travel provided. Please contact TTPI Liaison Office, Bldg. 112, Fort Mason, San Francisco, CA 94123 for applications. Telephone (415) 556-7065.

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THE CALIFORNIA HEALTH SERVICES CORPS has opportunities for primary care physicians in mountain, desert and agricultural areas of California. Malpractice coverage is provided in addition to state equivalent salary and benefits. Contact Rural Health Section, State Department of Health, 714 "P" Street, Room 476, Sacramento, Ca. 95814. (916) 322-4704.

STAFF PSYCHIATRISTS—The Fresno County Department of Health has two positions available in an innovative community-based total health care program. One position involves a team approach to rural and urban communities. Second involves services to a variety of clinical sites for providing acute mental health services. Located in the Central Valley close to San Francisco, Los Angeles, ocean, and the mountains. Salary range $39,684 and up, depending on experience, plus fringe benefits. California license and Board eligibility required by the end of the first year. Contact: James T. Stripe, MD, or Thomas E. Addison, LCSW, Fresno County Department of Health, P.O. Box 11867, Fresno, CA 93775 (209) 488-3731 or (209) 488-3927.

CALIFORNIA, SAN JOSE: Experienced, career-oriented Emergency Physicians wanted to join well-established group practicing at a university affiliated hospital and a large community hospital. Beautiful San Francisco Bay area location. Fee-for-service compensation. ACEP preferred. Contact: James B. Lane, MD at (408) 293-8881 or write: 1530 The Alameda, No. 28, San Jose, CA 95126.

(Continued on Page 34)

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With the award of a newly extended contract for our Saudi Arabian Health Care Project, Whittaker is offering unique opportunities to Board Certified Physicians with the following specialties

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UCLA SCHOOL OF MEDICINE

Department of Anesthesia seeks a Chairman of the Department of Anesthesiology at San Bernardino County Medical Center, its affiliate in San Bernardino, California. Board certification and California license essential. Salary open. Full medical liability coverage. Interested candidates should direct inquiries or submit credentials (including CV) to: **J. PHILIP LOGE, MD; Medical Center Director, SAN BERNARDINO COUNTY MEDICAL CENTER, 780 E. Gilbert, San Bernardino, CA 92404.**

Both the UNIVERSITY OF CALIFORNIA and SAN BERNARDINO COUNTY MEDICAL CENTER are Equal Opportunity, Affirmative Action Employers.

QUALICARE

a National Hospital Management Company has a number of communities in need of physicians. We have several types of practice opportunities available in California, Virginia, Alabama, Illinois and Mississippi. One such opportunity exists for an internist in Southern California. Located 75 Miles south of Los Angeles, this vital community offers proximity to both the coast and mountains/ski area, with excellent schools, churches, recreational and cultural activities. Guaranteed first year income, office space and household move is paid. If you would like a really rewarding practice in an area where you are needed and appreciated please send curriculum vitae to: **JOE ANN LINDSEY, QUALICARE, INC., P.O. Box 24189, New Orleans, LA 70184 or call collect at (504) 837-6456.**

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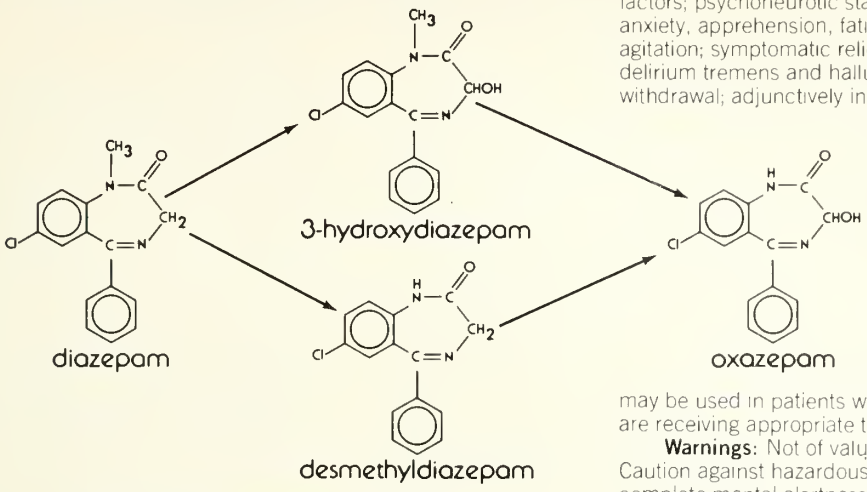
Complete coverage for hospital, clinic or office on "AS NEEDED" basis in Bay Area, So. Calif. and San Diego. Call or write to: P.O. Box 6275, Oakland CA 94603 (415) 763-0336; P.O. Box 1102, S. Monica, CA 90406 (213) 393-4267; P.O. Box 2828, S. Diego, CA 92112 (714) 231-0123.

A pharmacokinetic character all its own



Valium (diazepam) is a benzodiazepine with a distinctive pharmacokinetic profile

The pharmacokinetic profile of Valium is one of the characteristics that sets it apart from other benzodiazepines. Consider, in particular, the metabolic pathway of Valium. The three major metabolites of Valium exhibit significant pharmacologic activity—and so, of course, does the parent substance—diazepam itself. All combine to produce the characteristic clinical response seen with Valium. The response you have come to know, to want and to trust.

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2-mg, 5-mg, 10-mg scored tablets

a prudent choice in psychic tension and anxiety

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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(Continued from Page 32)

PHYSICIANS WANTED

THE DEPARTMENT OF FAMILY PRACTICE, UCLA School of Medicine, seeks an Associate physician for the Department of Family Practice at Kern Medical Center, its affiliate in Bakersfield, California. Board certification or eligibility in Family Practice or Internal Medicine required. Salary competitive, with full medical liability coverage. Interested candidates should direct inquiries, credentials, and curriculum vitae to Ramon H. Neufeld, MD, MPH, Chairman, Department of Family Practice, Kern Medical Center, 1830 Flower Street, Bakersfield, California 93305. Telephone (805) 323-7651. Both the University of California and Kern Medical Center are equal opportunity employers.

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BOARD CERTIFIED Family Practice or Internal Medicine to serve as Medical Director of an Independent Clinical Research Laboratory. Minimum 2 years post-certification practice desired. Salary commensurate with credentials, executive benefit package. Pleasant midwestern University community. Enclose curriculum vitae. Box 5945, Western Journal of Medicine, 731 Market Street, San Francisco, CA 94103.

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50-MAN MULTISPECIALTY CLINIC seeks second Otolaryngologist, Board Certified or eligible, to fill out active department located in pleasant coastal city. Contact W. Richard Ellis, Sansum Medical Clinic, Santa Barbara, CA 93102. (805) 682-2621.

PHYSICIANS
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ALLERGIST—Board Certified or Board Eligible—Appointment would encompass activities at our central campus and our newly established suburban clinics.

ANESTHESIOLOGIST—Director of Education—Board Certified anesthesiologist with experience in residency training programs. A qualified individual will be given the responsibility to reinstate and direct a three year residency program in anesthesiology.

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GENERAL SURGEON—Board Certified with 5-10 years experience, interested in either (1) general surgery, (2) intensive care, (3) head and neck, or (4) research as their area for concentration.

NEUROSURGEON—Board Certified or Board Eligible for a position in the Department of Neurosurgical Surgery.

ORTHOPEDIC SURGEON—Board Certified or Board Eligible—The appointment would encompass activities at central campus and newly established suburban clinics. Position entails major surgery and participation in teaching at the central campus as well as outpatient practice and minor surgical procedures performed at the suburban clinics.

OTOLARYNGOLOGIST—Board Certified or Board Eligible. Appointment would encompass activities at our central campus and newly established suburban clinics. Position entails surgery and participation in teaching at the central campus as well as outpatient practice and minor surgical procedures performed at the suburban clinics.

PSYCHIATRIST—Board Certified or Board Eligible—Instructorships available with major universities, positions available at main campus as well as suburban centers. Areas of concentration for interested individuals should lie in either (1) clinical outpatient, (2) liaison consulting, (3) crisis intervention.

RADIOLOGIST—Board Certified general diagnostic radiologist and an angiography specialist for main campus, suburban centers as well as major affiliate medical schools. The Department of Diagnostic Radiology is multi-facet in that it is composed of individual "centers" for general diagnostic activities, nuclear medicine activities, ultrasound activities, and most recently, computed tomograph procedure which includes both EMI head and EMI body scanner. The training program includes an accredited Residency Program and allied Health Science Education Program in the area of Nuclear Medicine, Radiologic Technology, and Ultrasound Technology.

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Interested parties should send their curriculum vitae in strict confidence. Write BOX NO. 5949, WESTERN JOURNAL OF MEDICINE, 731 MARKET ST., SAN FRANCISCO, CA 94103.

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CALIFORNIA—Board Certified Anesthesiologist for Chief, Anesthesia Section needed at VA Hospital, Livermore, CA. Ideal living, good climate and clean air. Malpractice insurance not needed. Position will be available in August. Salary dependent on experience and qualifications. Contact: Byron V. Whitney, MD, FACS, Chief, Surgical Service, Veterans Administration Hospital, Livermore, CA 94550, Tel: (415) 447-2560, Ext. 213.

ORTHOPEDIST needed—immediately—temporary or permanent. Salary negotiable. Contact Lynn T. Levy, MD, Box 46, Sun Valley, Idaho 83353. Call (208) 622-4526.

PHYSICIANS WANTED

OBSTETRICS/GYNECOLOGY: Board Certified or eligible. Join an 18 MD multispecialty group located on the San Francisco peninsula. Hospital across the street and near two university hospital centers. Quality housing, schools and recreation; competitive starting salary with early progression to full partnership. Send curriculum vitae to or telephone Ronald L. Schwartz, Administrator, San Mateo Medical Clinic, 23 Baldwin Avenue, San Mateo, CA 94401. Phone (415) 342-7771.

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SANTA BARBARA. Want third man in Family Practice Department large multispecialty Clinic. All professional expenses paid; meetings, travel allowance, etc. Prefer Board Certified. Write E. T. Everett, MD, P.O. Box 1200, Santa Barbara, CA 93102.

BUSY CENTRAL CALIFORNIA COAST OPHTHALMOLOGIST wants associate immediately. Send résumé. Write P.O. Box 309, Monterey, CA 93940.

ASSISTANT RESEARCH GASTROENTEROLOGIST—An opening is available for an Assistant Research Gastroenterologist with prior experience in the development of tumor associated antigen assays in biological specimens and also experienced in the development of studies on the role of nutrition in cancer and in the basic biochemistry of tumor antigens. This person must have a PhD degree in biochemistry and in nutrition and be thoroughly trained in standard physical-chemical methods including mass spectrometry, nuclear magnetic resonance and must be capable of developing new radioimmunoassays for viral and tumor antigens. In addition this person should be well trained in veterinary surgical procedures. Write Box 5954, Western Journal of Medicine, 731 Market Street, San Francisco, CA 94103.

RADIOLOGIST—California. Two openings, one in Nuclear Medicine, certified; one with primary interest in special procedures. UCSF-affiliated, 265-bed teaching hospital; department of 51; five radiologists associated in academically oriented clinical practice. Send CV to Justin L. Williams, MD, Chief of Radiology, Valley Medical Center, 445 S. Cedar Ave., Fresno, CA 93702, or phone (209) 453-5165.

GENERAL SURGEON—Board certified or eligible to join two other general surgeons in a 15-man multi-specialty group, Southern Idaho. A community of 25,000 people, large referral area, close to all varieties of outdoor recreation. Reply to Box 5952, Western Journal of Medicine, 731 Market Street, San Francisco, CA 94103.

WANTED—ALLERGIST—Outstanding opportunity with a group of internists—subspecialists for allergist with strong internal medicine qualifications. In semi-rural community, within sixty minutes of San Francisco. Send Curriculum Vitae, Box 5955, Western Journal of Medicine, 731 Market Street, San Francisco, CA 94103.

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SAN FRANCISCO—Immediately available established solo 25-year-old practice in Internal Medicine-Cardiology in San Francisco. Near University of California Medical Center. Contact: Box 5956, Western Journal of Medicine, 731 Market Street, San Francisco, CA 94103.

SITUATIONS WANTED

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ENDOCRINOLOGIST-INTERNIST—Certified both specialties seeks relocation with group or another endocrinologist in Southern California. Training and practice with university with wide endocrine exposure. Reply Box 5953, Western Journal of Medicine, 731 Market Street, San Francisco, CA 94103.

ANESTHETIST AVAILABLE San Francisco Area on free lance basis. Anesthesia Services (415) 391-3339.

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33-YEAR-OLD BOARD CERTIFIED PULMONARY PHYSICIAN with expertise in fiberoptic bronchoscopy desires partnership or hospital associated practice in California. Available September 1978. Contact John Donaldson, 13107 Beaver Terrace, Rockville, MD 20853.

(Continued on Page 36)

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(Continued from Page 35)

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An outstanding faculty has been invited to speak on Diagnostic and Therapeutic Radiology, Nuclear Medicine, Ultrasound and Computerized Axial Tomography. Small workshops in all disciplines are planned for the first day. The next two days will consist of formal lectures and roundtable discussions. The radiological technical exhibit (the second largest in the country) will be open all three days.

Speakers

Diagnostic Radiology

Gerald D. Dodd, MD, University of Texas
John L. Doppman, MD, The Clinical Center, National Institutes of Health
John R. Thornbury, MD, University of Michigan Medical Center
Bertram R. Girdany, MD, University of Pittsburgh
Eugene C. Klatte, MD, Indiana University School of Medicine
Alex Norman, MD, New York Hospital for Joint Disease and Medical Center

Ultrasound & Computerized Body Scanning

Frederick W. Sample, MD, UCLA Center for the Health Sciences

Nuclear Medicine

James H. Christie, MD, University of Iowa Hospitals and Clinics

Radiation Therapy–Oncology

William L. Caldwell, MD, Wisconsin Clinical Cancer Center
Willett F. Whitmore, Jr., MD, Memorial Sloan-Kettering Cancer Center
Stanley Order, MD, Johns Hopkins Hospital
Joseph R. Betino, MD, Stanford University Medical Center
Gianni Bonadonna, MD, Istituto Nazionale Tumori
Luther W. Brady, MD, Hahnemann Medical College

Registration ..... Fee of $100 includes two luncheons. $50 for residents (supporting letter from their staff is included). Workshops: $25 each.

Advance Registration... Nathan Green, MD, 15107 Vanowen Street, Van Nuys, CA 91405.

Hotel Accommodations Convention Manager, Century Plaza Hotel, Los Angeles, CA 90067.

Message Center..... Furnished by Pacific Telephone Co. Out-of-town calls will be received at (213) 277-1890 from 9 a.m. to 5 p.m.

HAWAII POST CONVENTION SEMINAR

January 29 through February 5, 1978, $695 per person includes air fare from Los Angeles, all inter-island transportation and accommodations. Registration fee is $100. The faculty will cover topics shown above, and the week long seminar will be on the islands of Oahu (Honolulu Ilikai) and Maui (Maui Intercontinental).

Faculty: Doctors Dodd, Sample, Thornbury, Girdany and Norman.

CONTINUING MEDICAL EDUCATION

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THIS LISTING of continuing education programs in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 146. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

CANCER

November 18-19—**Endocrine Aspects of Cancer: New Perspectives.** Mt. Zion Hospital and Medical Center, San Francisco. Friday-Saturday. Contact: Ann Raisbeck, Dept. of Med. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2401.

December 3—**Physicians' Symposium on the Psychosocial Care of the Cancer Patient.** American Cancer Society, Alameda County Unit, at Claremont Hotel, Berkeley. Saturday. Contact: Robert Wooster, Ed. Dir., ACS, 1212 Broadway, Suite 612, Oakland 94602. (415) 832-7012.

December 7—**Cancer of the Pancreas and Bile Ducts—Current Status of Diagnosis and Treatment.** Hospital of the Good Samaritan, Los Angeles. Wednesday. 7 hrs. Contact: Janie Sternal, CME Coordinator, Hosp. of the Good Samaritan, 616 S. Witmer, Los Angeles 90017. (213) 488-8123.

January 25—**Breakthroughs in Lymphomas and Leukemias.** Hospital of the Good Samaritan, Los Angeles. Wednesday. 7 hrs. Contact: J. S. Bonorris, MD, Dir., Hematology Oncology, Hosp. of the Good Samaritan, 616 S. Witmer, Los Angeles 90017. (213) 488-8588.

January 27-28—**Cancer Update. A Clinical Approach to Diagnosis and Treatment of Common Malignancies—Breast, Colon, Lung and Prostate.** Peralta Hospital at Claremont Hotel, Berkeley. Friday-Saturday. Contact: Tish Hammerlee, Peralta Hosp., 450 30th St., Oakland 94609. (415) 451-4900, ext. 264.

January 30-31—**Cancer.** USC. Monday-Tuesday.

March 9-12—**Modern Concepts in Oncology.** UCLA at Canyon Hotel, Palm Springs. Thursday-Sunday.

March 10-12—**Cancer Endoduriethérapy.** USC at Hotel Bonaventure, Los Angeles. Friday-Sunday. 22 hrs.

March 27-31—**Cancer.** STAN. Monday-Friday. 27 hrs. $265.

EMERGENCY MEDICINE

December 8-9—**Advances in Emergency Medicine—Metabolic Emergencies.** UCSF. Thursday-Friday.

December 12-16—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Islandia Hotel, San Diego. Monday-Friday.

January 23-27—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Town and Country Convention Center, San Diego. Monday-Friday. 40 hrs. $325.

January 23-27—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

January 30-February 3—**Emergency Medicine.** UCLA at Beverly Hilton Hotel, Beverly Hills. Monday-Friday.

February 26-March 3—**Emergency Medical Care Symposium II.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday. $175.

March 20-24—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday. 40 hrs. $325.

April 3-7—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $325.

April 15-22—**Emergency Medicine.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week. 29 hrs. $300.

MEDICINE

November 17-19—**Unusual Problems in Pulmonary Disease.** USC at Erawan Gardens, Palm Springs. Thursday-Saturday.

November 26-December 3—**Lymphoproliferative Disorders.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

December 2-3—**Current Concepts in Renal Disease—7th Annual Medical Staff Symposium.** Daniel Freeman Hospital at Hyatt House Hotel, Los Angeles. Friday-Saturday. 9 hrs. $80. Contact: Donald Dennis, PhD, Dir. of Med. Ed., Daniel Freeman Hosp., 333 N. Prairie, Inglewood 90301. (213) 674-7050, ext. 127.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

December 2-4—**Advances in Heart Disease—1978.** American College of Cardiology at Fairmont Hotel, San Francisco. Friday-Sunday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Division of Continuing Education, ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

December 5-9—**Advances in Diagnosis and Treatment in Clinical Medicine.** American College of Physicians, Harbor General Hospital and St. Mary's Medical Center at Hyatt House Hotel, Los Angeles. Monday-Friday. Contact: Registrar, ACP, 4200 Pine St., Philadelphia, PA 19104.

December 7—**Current Data on the Epidemiology and Clinical Management of Essential Hypertension—Dinner Meeting/Scientific Program.** L. A. Soc. of Internal Medicine at L. A. County Medical Assn., Los Angeles. Wed. 1½ hrs. $7.50. Contact: Thomas T. Yoshikawa, MD, Prog. Chr., LASIM, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

December 10—**Pulmonary Artery Catheters and Ventilators.** PMC. Saturday. 6 hrs. $300.

December 11—**Peripheral Vascular Disease: A Multidisciplinary Challenge—9th Annual Symposium.** UCLA and Granada Hills Community Hospital at Calif. State Univ., Northridge. Sunday. 6 hrs. $30.

December 12—**Current Concepts in Ileitis and Colitis.** UCD at Red Lion Motor Inn, Sacramento. Monday.

December 14—**Degenerative Diseases of the Aorta—3rd Annual Lyman A. Brewer III Cardiothoracic Symposium.** White Memorial Medical Center at Century Plaza Hotel, Century City. Wednesday. 8 hrs. $50. Contact: Howard Whigman, PhD, Coor., Cont. Med. Ed., White Memorial Med. Ctr., 1720 Brooklyn Ave., Los Angeles 90033.

January 4-March 15—**Nights at UCLA: Infectious Diseases for the Practicing Internist.** Wednesdays; 7:30-9:30 p.m. 22 hrs. $200.

January 11—**Management of Arrhythmias.** LLU. Wednesday. 4 hrs. $25.

January 13-14—**Annual Allergy Symposium.** Southern California Permanente Medical Group at Beverly Hilton Hotel, Beverly Hills. Friday-Saturday. Contact: Shirley Gach, So. Calif. Permanente Med. Group, 4900 Sunset Blvd., Room 6014, Los Angeles 90027. (213) 667-4241.

January 14-15—**Practical Pulmonary Diseases for the Primary Care Physician.** UCLA. Saturday-Sunday. 14 hrs. $140.

January 20-21—**Stress Testing: A New Look Forward to New Developments—Backward to Old Concepts.** American College of Cardiology at Memorial Hospital Medical Center, Long Beach. Friday-Saturday. Contact: Miss Mary Ann McInerny, Dir., Extramural Programs Dept., Div. of Cont. Ed., ACC, 911 Old Georgetown Rd., Bethesda, MD 20014.

January 21—**Systemic Disease/Eye, Mouth, Skin Manifestations.** See Of Interest to All, January 21.

January 24-27—**Present Concepts in Internal Medicine.** American College of Physicians at Letterman Army Medical Center, San Francisco. Tuesday-Friday. Contact: Registrar, ACP, 4200 Pine St., Philadelphia, PA 19104.

January 25-27—**Advances in Neurology.** UCSF at Hyatt on Union Square, San Francisco. Wednesday-Friday.

January 27-29—**New Frontiers on the Relationships of Lipids, Lipoproteins and the Arterial Wall in Cardiovascular Disease.** UC Extension, Berkeley, and UCSF at Hyatt on Union Square, San Francisco. Friday-Sunday. 12 hrs. $150. Contact: Medical Symposia, Div. of Letters and Sciences, UC Extension, Berkeley 94720. (415) 642-1061.

February 3-4—**Allergy.** STAN. Friday-Saturday. $80.

February 7-10—**Your Consultant Speaks—A Multidisciplinary Course for Dermatologists.** STAN at Lake Tahoe. Tuesday-Friday. 12 hrs. $225; $100 for residents and those in training.

February 15-17—**Topics in Gastroenterology.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday.

DEPARTMENT OF THORACIC AND CARDIOVASCULAR SURGERY

WHITE MEMORIAL MEDICAL CENTER

and

LOMA LINDA UNIVERSITY SCHOOL OF MEDICINE

announce

The Third Annual Lyman A. Brewer III Cardiothoracic Symposium

ON

DEGENERATIVE DISEASES OF THE AORTA

WEDNESDAY, DECEMBER 14, 1977

8:30 a.m. to 5:30 p.m.

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Avenue of the Stars

LOS ANGELES, CALIFORNIA 90067

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ALFRED H. F. LUI, MD, Assistant Clinical Professor of Surgery, Loma Linda University School of Medicine; Attending Staff, Department of Thoracic and Cardiovascular Surgery, White Memorial Medical Center

Honored Guest Speaker

PROFESSOR CHARLES DUBOST, Clinique Chirurgicale Cardio-Vasculaire, Hopital Broussais, Paris, France

Guest Faculty

DAVID H. BLANKENHORN, MD, Professor of Medicine, University of Southern California School of Medicine; Director of Cardiology, Los Angeles County/University of Southern California Medical Center, Los Angeles, California

ALBERT E. HIRST, MD, Professor of Pathology, Loma Linda University School of Medicine, Loma Linda, California

J. FRASER MUSTARD, MD, PhD, Dean, Faculty of Health Sciences, McMaster University Health Science Center, Hamilton, Ontario, Canada

HASSAN NAJAFI, MD, Professor and Chairman, Department of Cardiovascular-Thoracic Surgery, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois

DANIEL STEINBERG, MD, PhD, Professor of Medicine, Head, Division of Metabolic Disease, University of California, San Diego School of Medicine, La Jolla, California

MYRON W. WHEAT, JR, MD, Clinical Professor of Surgery, University of Louisville School of Medicine, Louisville, Kentucky; Chairman, Department of Surgery, Chief, Thoracic and Cardiovascular Surgery, Diagnostic Clinic, Largo and St. Petersburg, Florida.

EDWIN J. WYLIE, MD, Professor and Vice-Chairman, Department of Surgery, University of California, San Francisco, School of Medicine, San Francisco, California

Information

REGISTRATION FEES: Physicians $75.00; Residents, Interns, Registered Nurses and Others $35.00 (includes luncheon, refreshment breaks and exhibits). Make checks payable to: Lyman A. Brewer III Symposium

Mail to: **COORDINATOR, CONTINUING MEDICAL EDUCATION**
WHITE MEMORIAL MEDICAL CENTER
1720 BROOKLYN AVENUE, BOX 137
LOS ANGELES, CALIFORNIA 90033

Registration by telephone:
Telephone: (213) 263-6100

Credit

This is an approved program of Continuing Medical Education: CMA and AMA 8½ hours category I credit, CNA 8½ contact hours for relicensure, AMSECT 10 points toward reclassification

February 23-25—**Advances in the Diagnosis and Therapy of Cardiovascular Disease—1978.** American College of Cardiology at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed. ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 3—**Diabetes Program—5th Annual.** UCD at Red Lion Motor Inn, Sacramento. Friday.

March 3-4—**Diagnosis and Management of Aphasia.** PMC at Presbyterian Hospital, San Francisco. Friday-Saturday. 12 hrs. $100.

March 6-9—**American College of Cardiology—27th Annual Scientific Session.** Disneyland Hotel, Anaheim. Monday-Thursday. Contact: Patrick Ziarnik, Dir., Annual Sci. Session Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 10-11—**Clinical Cardiology.** American College of Cardiology at Kauai Surf Hotel, Kauai, Hawaii. Friday-Saturday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 16-19—**Viral Hepatitis.** UCSF at Hilton Hotel, San Francisco. Thursday-Sunday. 26 hrs. $145.

March 23-25—**Immunology and Allergy Conference—2nd Annual.** UCSD at Hilton Hotel, San Diego. Thursday-Saturday.

March 28-31—**Consultant's Course in Dermatology—6th Annual.** UCSF. Tuesday-Friday. $250.

March 31-April 1—**Seminar on Thrombosis.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. 10 hrs. $75.

April 3-12—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. 10 days. Contact: Miss Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 3-14—**Intensive Review of Internal Medicine.** USC. 12 days.

April 12-June 14—**Nephrology for the Practicing Internist.** UCLA. Wednesday evenings; 10 weeks.

April 14-15—**Arthroscopy.** UCLA. Friday-Saturday. 12 hrs. $315.

April 19-21—**Echocardiographic Solutions to Clinical Cardiovascular Problems.** American College of Cardiology at UCLA. Wednesday-Friday. Contact: Miss Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

OBSTETRICS AND GYNECOLOGY

December 1-3—**High-Risk Pregnancy—2nd Annual Postgraduate Course.** Memorial Hospital Medical Center of Long Beach at Canyon Hotel, Palm Springs. Tuesday-Saturday. 14½ hrs. $200. Contact: Exec. Sec., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 14-21—**Perinatal Medicine.** USC at Royal Lahaina, Maui, Hawaii. One week. 21 hrs. $300.

January 19-21—**Pregnancy and Hypertension.** DREW at Hyatt House Hotel, Los Angeles. Thursday-Saturday. 20 hrs.

January 26-May 25—**Recent Advances in Obstetrics and Gynecology—2nd Annual.** UCLA. Thursday evenings. 32 hrs. $310.

January 28-30—**Comprehensive Laparoscopy.** UCSD at Kona Kai Club, San Diego. Saturday-Monday. 16 hrs. $375.

February 11-12—**Obstetrical and Gynecological Forum.** L. A. Obstetrical and Gynecological Society at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. Contact: Ms. Dee Davis, Exec. Sec., L. A. Obstetrical and Gynecological Society, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

March 9-10—**Gynecological Urology Seminar.** See Surgery, March 9-10.

(Continued on Page 42)

Tablets
Percocet®-5 (II)

DESCRIPTION Each tablet of PERCOCET®-5 contains 5mg oxycodone hydrochloride (WARNING May be habit forming), 325mg acetaminophen (APAP)

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET®-5, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET®-5 is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET®-5 should be cautioned accordingly

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET®-5 may exhibit an additive CNS depression When such combined therapy is contemplated, the dose of one or both agents should be reduced

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCOCET®-5 should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCOCET®-5 should not be administered to children.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries

Acute abdominal conditions The administration of PERCOCET®-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions

Special risk patients PERCOCET®-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET®-5 is given orally The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCOCET®-5 may be additive with that of other CNS depressants. See WARNINGS.

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November 1977 EDO 1480

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Acetaminophen with the narcotic difference

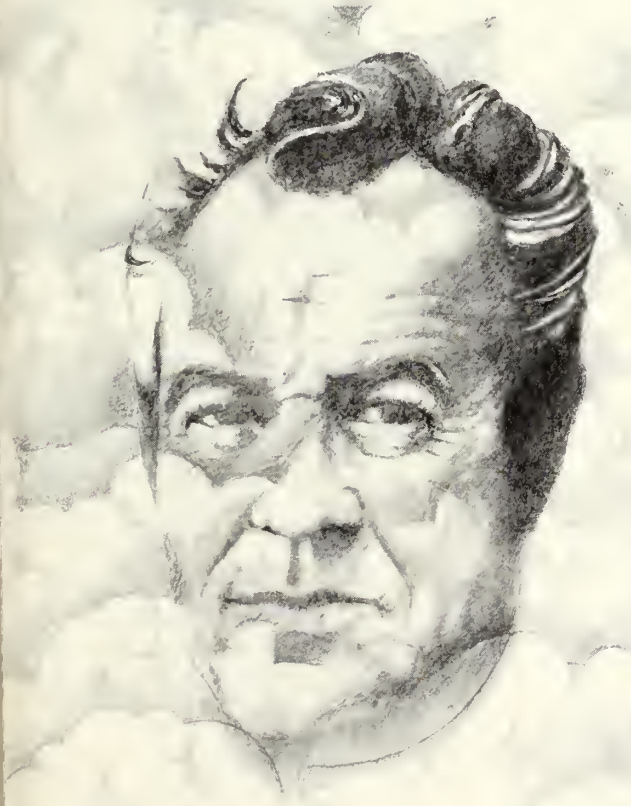
Reliable oral narcotic analgesia...

The narcotic component in PERCOCET®-5 is oxycodone, which is readily absorbed and provides dependable oral analgesia—usually within 15 to 30 minutes. Oxycodone can produce drug dependence of the morphine type and should be prescribed with the same degree of caution appropriate to the use of other narcotic-containing medications.

...aspirin free

Acetaminophen is a non-narcotic analgesic widely used for aspirin-sensitive patients. Equivalent to aspirin in analgesia, it complements the pain relief provided by oxycodone.

The usual dose of PERCOCET®-5 is one tablet every six hours, providing convenience and economy for your patients. PERCOCET®-5 is ideally suited for your patients with aspirin sensitivity, with hemostatic disturbance, with peptic ulcer or on anticoagulation therapy.



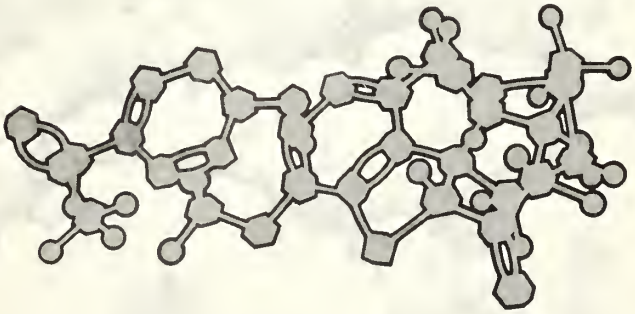
Tablets

Percocet®-5

each scored tablet contains 5 mg oxycodone HCl (WARNING: may be habit forming) and 325 mg acetaminophen

CII

When aspirin is contraindicated.



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Please see facing page for Brief Summary of prescribing information.

(Continued from Page 40)

April 10-12—**Antenatal Assessment of the Fetus From Conception to Delivery.** UCSD at Vacation Village, San Diego. Monday-Wednesday. 21 hrs. $150.

PEDIATRICS

November 15—**Pediatrics—Common Office Problems and Treatment.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Chr., Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

December 3—**Practical Aspects of Sports Medicine for Pediatricians.** American Academy of Pediatrics, Calif. Chapter I, Dist. IX, at Union Square Holiday Inn, San Francisco. Saturday. Contact: Martin Gershman, MD, 595 Buckingham Way, San Francisco 94132.

December 10—**Infant Feeding: Human Milk in the Modern World.** UCLA. Saturday. 9½ hrs. $35.

January 12-14—**General Pediatrics.** American Academy of Pediatrics at Kona Surf Hotel, Kailua-Kona, Hawaii. Thursday-Saturday. Contact: L. J. Nagel, Dept. of Cont. Ed., AAP, P.O. Box 1034, Evanston, IL 60204. (312) 869-4255.

January 25-29—**Winter Ski and Study Symposium—3rd Annual.** American Academy of Pediatrics, District IX, Chapter 2, at Mammoth Mountain. Wednesday-Sunday. $145, members; $160, non-members. Contact: Calif. Chapter 2, AAP, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

January 26-28—**Troubled Youth.** See Psychiatry, January 26-28.

January 27-29—**Pediatric Anesthesiology.** See Surgery and Anesthesiology, January 27-29.

January 28-29—**Pediatrics for the Primary Physician: A Practical Update.** See Of Interest To All, January 28-29.

February 10—**Pediatric Otolaryngology.** See Surgery and Anesthesiology, February 10.

March 17-19—**Combined Southern California Pediatric Postgraduate Meeting—8th Annual.** American Academy of Pediatrics, District IX, Chapter 2, at Riviera Hotel, Palm Springs. Friday-Sunday. $135, members; $150, non-members. Contact: Calif. Chapter 2, AAP, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

April 5-7—**General Pediatrics.** American Academy of Pediatrics at Century Plaza Hotel, Los Angeles. Wednesday-Friday. Contact: L. J. Nagel, Cont. Ed. Programs, AAP, P.O. Box 1034, Evanston, IL 60204. (312) 869-4255.

April 7-8—**Common Problems in Ambulatory Pediatrics.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday.

April 8-13—**American Academy of Pediatrics—Spring Session.** Century Plaza Hotel, Los Angeles. Saturday-Thursday. Contact: L. J. Nagel, Cont. Ed. Programs, AAP, P.O. Box 1034, Evanston, IL 60204. (312) 869-4255.

PSYCHIATRY

January 3-April 4—**Intensive Review Course: American Board of Psychiatry and Neurology.** UCD. Tuesdays; 7:00-10:00 p.m. 42½ hrs. $275.

January 10-March 21—**Intensive Review of Psychiatry.** USC. Tuesday evenings.

January 20-22—**Psychoanalytically Oriented Psychotherapy: A Retrospective.** UCSF. Friday-Sunday. 12 hrs. $45.

January 26-28—**Troubled Youth.** USC at Vacation Village, San Diego. Thursday-Saturday.

January 27-28—**Practical Psychiatry.** PMC at Presbyterian Hospital, San Francisco. Friday-Saturday. 12 hrs. $125.

January 29-February 3—**Midwinter Program in Continuing Education for Psychiatrists.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday.

February 8—**Overview of Newer Approaches for Troubled Patients.** LLU. Wednesday. 4 hrs. $25.

April 15-16—**Stress: Psychological Management.** UCLA at Santa Cruz. Saturday-Sunday.

RADIOLOGY AND PATHOLOGY

December 20—**Diagnostic X-Ray Including Cat Scans.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Chr., Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

January 16-20—**Computed Tomography.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. $295.

January 17—**Updating Radiation Therapy.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Chr., Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

January 27-29—**Los Angeles Radiological Society—30th Annual Mid-Winter Meeting.** Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Nathan Green, MD, 15107 Vanowen St., Van Nuys 91405.

January 27-29—**New Frontiers on the Relationships of Lipids, Lipoproteins and the Arterial Wall in Cardiovascular Disease.** See Medicine, January 27-29.

February 19-24—**Interpretative Enzymology.** UCSD at Sheraton Inn-Airport, San Diego. Sunday-Friday. 25 hrs.

February 21—**Clinical Laboratory Tests: Results, Clinical Application and New Laboratory Tests.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Chr., Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

March 4-5—**Diagnostic Nuclear Imaging.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday. 9 hrs. $100.

March 5-10—**Medical Imaging in the High Sierra.** American College of Medical Imaging and American Institute of Ultrasound in Medicine at Sahara Tahoe Hotel, Lake Tahoe. Sunday-Friday. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

March 6-10—**Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. $275.

March 11-12—**A Practical Course in B-Scan Ultrasound.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday. 9 hrs. $125.

April 9-14—**American College of Radiology—Annual Meeting and Categorical Course.** Town and Country Hotel, San Diego. Sunday-Friday. Contact: Ms. Sheila Aubin, Meeting Manager, ACR, 20 N. Wacker Dr., Chicago, IL 60606. (312) 236-4963.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 15 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY AND ANESTHESIOLOGY

November 17-18—**Legg-Calve-Perthes Symposium.** Orthopaedic Hospital, Los Angeles, at Airport Park Hotel, Inglewood. Thursday-Friday. $200. Contact: Med. Ed. Dept., Orthopaedic Hospital, 2400 S. Flower St., Los Angeles 90007.

November 18-19—**Strabismus.** PMC. Friday-Saturday. 16 hrs.

November 19—**Glaucoma Surgery Workshop.** Jules Stein Eye Institute and UCLA. Saturday. 8 hrs. $200. Contact: Lu Hendricks, Academic Prog. Admin., Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

November 19-20—**American Society of Anesthesiologists—Regional Refresher Course.** Sahara Hotel, Lake Tahoe. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

November 30-December 2—**Annual Ophthalmology Program.** UCSF. Wednesday-Friday.

November 30-December 2—**Applied Biomechanics for Orthopedic Surgeons.** UCLA. Wednesday-Friday. 23 hrs. $200.

December 2-4—**ENG Workshop.** PMC at Ilikai Hotel, Honolulu. Friday-Saturday. 24 hrs. $395.

December 3—**Emergency Anesthesia.** Sacramento Valley Anesthesia Society; UCD; Calif. Society of Anesthesiologists at Red Lion Motor Inn, Sacramento. Saturday. $50. Contact: John H. Eisele, MD, Dept. of Anesthesiology. UCD Sch. of Med., Davis 95616. (916) 752-2703.

December 14—**Treatment of Parkinsonism and Modern Concepts.** LLU. Wednesday. 4 hrs. $25.

January 5-7—**Anesthesia Update '78.** UCSD at Hotel Del Coronado, Coronado. Thursday-Saturday. 15 hrs. $150.

January 16-20—**Otologic Surgery—13th Annual Course.** Ear Research Institute, Los Angeles. Monday-Friday. 45 hrs. $500. Contact: F. H. Linthicum, Jr., MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

January 20-21—**Hand Injuries and Infections.** PMC at Presbyterian Hospital, San Francisco. Friday-Saturday. 9 hrs. $150.

January 21—**Ophthalmic Plastic Surgery.** Jules Stein Eye Institute and UCLA. Saturday. 8 hrs. $200. Contact: Lu Hendricks, Academic Prog. Admin., Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

January 22-26—**Ophthalmology and Otolaryngology—47th Annual Mid-Winter Clinical Convention.** The Research Study Club of Los Angeles, Inc., at Hilton Hotel, Los Angeles. Sunday-Thursday. 28 hrs. $175. Contact: Mr. Richard Pruter, Exec. Sec., P. O. Box 49412, Los Angeles 90049. (213) 879-0143.

January 27-29—**Pediatric Anesthesiology—16th Clinical Conference.** Children's Hospital of Los Angeles at Hilton Hotel, Los Angeles. Friday-Sunday. 15 hrs. $135. Contact: Wayne Herbert, MD, Children's Hosp., 4650 Sunset Blvd., Los Angeles 90027. (213) 660-2450, ext. 2262.

February 3-4—**Phacoemulsification Surgery Course.** Jules Stein Eye Institute and UCLA. Friday-Saturday. $300. Contact: Lu Hendricks, Academic Prog. Admin., 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

February 5-8—**Surgical Anatomy—19th Annual Theodor Billroth Course.** LLU. Sunday-Wednesday. 32 hrs. $200.

February 10—**Pediatric Otolaryngology.** USC. Friday.

February 28-March 3—**Diagnosis and Management of Acoustic Neuromas and Skull Base Tumors.** Ear Research Institute, Los Angeles. Tuesday-Friday. 32 hrs. $400. Contact: William F. House, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

March 3-4—**Development and Management of Aphasia.** See Medicine, March 3-4.

March 8—**General Surgery Seminar.** LLU. Wednesday. 4 hrs. $25.

March 9-10—**The Orbit: Diagnostic Approaches and Management Decisions.** PMC at Stanford Court Hotel, San Francisco. Thursday-Friday. $225.

March 9-10—**Gynecological Urology Seminar.** American Urological Association at Airport Marina Hotel, Los Angeles. Thursday-Friday. 16 hrs. $180. Contact: Gynecological Urology Seminar, c/o Joseph J. Kaufman, MD, UCLA Med. Ctr., Div. of Urology, Los Angeles 90024.

March 11—**Cataract Surgery and Intraocular Lens.** Jules Stein Eye Institute and UCLA. Saturday. 8 hrs. $225. Contact: Lu Hendricks, Academic Prog. Admin., Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

March 12-17—**Anesthesiology 1978—4th Annual Winter Meeting.** Anesthesiology Educational Foundation and Calif. Society of Anesthesiologists at Mammoth Lakes. Sunday-Friday. 20 hrs. Contact: Ronald L. Katz, MD, Dept. of Anesthesiology, UCLA School of Medicine, Los Angeles 90024.

March 19-23—**International Anesthesia Research Society—52nd Congress.** Hilton Hotel, San Francisco. Sunday-Thursday. Contact: B. B. Sankey, MD, Exec. Sec., IARS, 3645 Warrensville Center Rd., Cleveland, OH 44122. (216) 295-1124.

March 21—**Urology—Common Office Problems and Treatment.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Chr., Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

March 29-April 2—**Controversial Areas in Surgery—15th Annual Seminar.** UCLA at Canyon Hotel, Palm Springs. Wednesday-Sunday. 13 hrs. $195.

March 30-31—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs.

April 2-6—**Vascular Surgery—6th Annual Symposium.** UCLA at Canyon Hotel, Palm Springs. Sunday-Thursday.

April 12-14—**Maxillofacial Trauma—Soft Tissues Reconstruction and Facial Nerve Injury.** UCSF. Wednesday-Friday.

April 13-15—**General Surgery—Annual Course.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday.

April 14-21—**California Society of Anesthesiologists—2nd Hawaii Seminar.** Hyatt Regency Hotel, Waikiki-Honolulu. One week. 20 hrs. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

April 15-22—**Orthopedic Review.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

April 18—**Orthopaedics—Common Office Problems and Treatment.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

April 20-21—**Current Concepts of Macular Structure, Function and Disease—9th Annual Jules Stein Lecture and Postgraduate Seminar.** Jules Stein Eye Institute and UCLA at Century Plaza Hotel, Los Angeles. Thursday-Friday. $225. Contact: Lu Hendricks, Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

April 29-May 6—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $275.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

November 18-20—**Sexual Problems in Medical Practice.** USC at Gene Autry Hotel, Palm Springs. Friday-Sunday.

November 18-22—**Gerontological Society—Annual Scientific Meeting.** Co-sponsored by UCSF. Hilton Hotel, San Francisco. Friday-Tuesday. 25 hrs. Contact: E. Jane White, Gerontological Society, 2728 Durant Ave., Berkeley 94704. (415) 848-7604.

December 1-4—**The Health Professional and Sexuality: An Essential Dimension in Patient Care.** UCD at Hyatt Lake Tahoe, Incline Village. Thursday-Sunday.

December 5-9—**Advances in Diagnosis and Treatment in Clinical Medicine.** See Medicine, December 5-9.

December 9-11—**Clinical Toxicology, Pharmacology and Carcinogenic Hazards.** UC Extension, Berkeley, and UCSF at Hyatt Regency Hotel, San Francisco. Friday-Sunday. 12 hrs. $150. Contact: Medical Symposia, Div. of Letters and Sciences, UC Extension, Berkeley 94720. (415) 642-1061.

December 14—**Treatment of Parkinsonism.** See Surgery, December 14.

January 14-15—**Practical Pulmonary Diseases for the Primary Care Physician.** See Medicine, January 14-15.

January 18-20—**Infectious Disease.** USC. Wednesday-Friday.

January 19-20—**Biofeedback Techniques in Physical Medicine and Rehabilitation.** Herrick Memorial Hospital, Berkeley. Thursday-Friday. Contact: Marie Ham, Med. Staff Sec., Herrick Mem. Hosp., 2001 Dwight Way, Berkeley 94704. (415) 845-0130, ext. 418.

January 19-21—**Medical Aspects of Aging.** UCLA at Sheraton Universal Hotel, Universal City. Thursday-Saturday.

January 21—**Systemic Disease/Eye, Mouth, Skin Manifestations.** Continuing Medical Education/San Luis Obispo Consortium at Hilton Inn, San Luis Obispo. Saturday. 5 hrs. $25 for non-consortium members. Contact: Billy Mounts, MD, Chr., CME/SLO Consortium, P.O. Box 319, San Luis Obispo 93406.

January 23-27—**Therapy: Principles and Use of Drugs.** STAN. Monday-Friday. 27 hrs. $265.

January 28-29—**Pediatrics for the Primary Physician: A Practical Update.** UCLA. Saturday-Sunday. 10 hrs. $135.

January 30-February 4—**Family Practice Refresher Course—9th Annual.** UCI at Newporter Inn, Newport Beach. Monday-Saturday.

February 2-3—**Family Planning, Human Sexuality and Venereal Disease.** DREW at Hyatt House, Long Beach. Thursday-Friday. 15 hrs.

February 3-5—**American Medical Association—Regional Program.** Sahara Tahoe Hotel, Stateline. Friday-Sunday. Contact: UCD or Mr. G. K. Jewett, Dir., Dept. of Cont. Ed. Seminars, AMA 535 N. Dearborn St., Chicago 60610. (312) 751-6000.

February 8-11—**Primary Care—Current Management of Common Office Problems.** UCSF at Golden Gate Holiday Inn, San Francisco. Wednesday-Saturday.

February 10-11—**Alcoholism Update—4th National Seminar.** Vista Hill Foundation at Hotel del Coronado, Coronado. Friday-Saturday. 9 hrs. Contact: Virginia Everett, Dir., Public Relations, Vista Hill Foundation, 7798 Starling Dr., San Diego 92123. (714) 278-6761.

February 10-12—**Headaches: Evaluation and Management.** UCLA at Beverly Hilton Hotel, Beverly Hills. Friday-Sunday. 18 hrs.

February 12-13—**Workshop on Alcoholism—A Clinical Approach for Health Professionals.** UCSD at Sheraton Inn-Airport, San Diego. Sunday-Monday. 13 hrs.

February 13-17—**LLU Alumni Association—Annual Postgraduate Convention.** LLU. Monday-Friday.

February 15-17—**Course for Physicians in Family Practice—27th Annual.** Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Ann Raisbeck, Dept. of Med. Ed., Mt. Zion Hospital and Med. Ctr., P. O. Box 7921, San Francisco 94120. (415) 567-6600, ext 2401.

February 16-17—**Selected Topics in Geriatric Medicine.** STAN and Palo Alto VA Hospital at Stanford. Thursday-Friday.

February 20-24—**Caring for Older Persons.** Medical Communications and Services Assn. at Kona Surf Hotel, Kailua, Kona, Hawaii. Monday-Friday. 31 hrs. $195. Contact: MCSA, 315 University District Bldg., 1107 N. E. 45th St., Seattle, WA 98105. (206) 633-0505.

February 27-March 3—**Basic Science for Clinicians.** STAN. Monday-Friday. 25½ hrs. $265.

February 27-March 3—**Clinical Management of Sexual Problems.** Medical Communications and Services Assn. at Sheraton Hotel, Molokai, Hawaii. Monday-Friday. 30 hrs. $195. Contact: MCSA, 315 University District Bldg., 1107 N. E. 45th St., Seattle, WA 98105. (206) 633-0505.

March 4—**Controversies in Applied Immunotherapy.** UCSF at Children's Hospital, San Francisco. Saturday.

March 4-5—**Current Trends in the Management of Common Genetic Disorders.** UCLA. Saturday-Sunday.

March 6-8—**Diagnosis, Treatment and Prevention of Genetic Disease.** American College of Physicians; Harbor Gen. Hospital; Nat'l Foundation-March of Dimes at Riviera Hotel, Palm Springs. Monday-Wednesday. Contact: Registrar, ACP, 4200 Pine St., Philadelphia 19104.

March 7-May 23—**Bedside Clinics.** USC at Children's Hospital, Los Angeles. Tuesday evenings.

March 8-10—**Neurology for Non-Neurologists.** UCSD at Hilton Hotel, San Diego. Wednesday-Friday. 22 hrs.

March 10-12—**American Medical Association—Regional Seminar.** Newporter Inn, Newport Beach. Friday-Sunday. Contact: G. K. Jewett, Dir., Dept. of Cont. Ed. Seminars, AMA, 535 N. Dearborn St., Chicago 60610. (312) 751-6000.

March 11-12—**Liaison Psychiatry.** UCLA. Saturday-Sunday. 14 hrs.

March 14-18—**Sports Medicine for the Primary Physician.** Univ. of Hawaii School of Medicine at Princess Kaiulani Hotel, Honolulu. Tuesday-Saturday, 18 hrs. $200. Contact: Univ. of HI Sports Medicine Course, Hawaii Conference Services, P.O. Box 22670, Honolulu 96822.

March 15-18—**Critical Care Medicine.** USC at MGM Grand Hotel, Las Vegas. Wednesday-Saturday.

March 17-19—**Family Practice—Intensive Review.** DREW. Friday-Sunday.

March 17-22—**California Medical Association—107th Annual Session.** Fairmont Hotel, San Francisco. Friday-Wednesday. Contact: Linda Ramsey, CMA.

April 2-7—**Electrophysiology.** USC at Erawan Gardens, Palm Springs. Sunday-Friday.

April 8-9—**Stress: Medical Management.** UCLA at Palm Springs. Saturday-Sunday. 14 hrs.

April 12—**The Prostate.** LLU. Wednesday. 4 hrs. $25.

April 17-19—**Stress Workshop.** UCLA at Yosemite. Monday-Wednesday. 15 hrs.

April 22-23—**Practical Dermatology for the Primary Care Physician.** UCLA. Saturday-Sunday.

April 22-29—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

April 29-30—**Sports Medicine.** UCLA. Saturday-Sunday.

Audio-Digest Foundation. A nonprofit educational subsidiary of the California Medical Association. Twice-a-month tape-recorded summaries of leading national meetings. Services by subscription in: Anesthesiology, Family Practice, Internal Medicine, Obstetrics/Gynecology, Ophthalmology, Otorhinolaryngology, Pediatrics, Psychiatry, Surgery. ($90.00 per year for 24 one-hour cassettes or reels.) New catalog of lectures and panel discussions in all areas of medical practice also available, as well as cassette album condensations of the following 1977 specialty meetings: postgraduate courses from the annual meeting of the American Psychiatric Assn., workshops from the annual meeting of the American College of Physicians, and postgraduate courses from the annual sessions of the American College of Obstetricians and Gynecologists. For further information on subscriptions, catalogs and special courses, contact Mr. Claron L. Oakley, Editor, 1577 E. Chevy Chase Dr., Glendale 91206.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Physician-in-Residence Preceptorship in Pulmonary Disease. USC, Pulmonary Disease Section, Dept. of Medicine and Postgraduate Medical Education. One month or more, by arrangement. Opportunity for practicing physician to achieve specified knowledge and skills in adult pulmonary medicine. Contact: Oscar J. Balchum, MD, PhD, USC.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Department of Internal Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen R. Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, 97201.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

December 1—**Family Practice Educational Program: Empathetic Understanding.** Main Auditorium, Woodland Park Hospital, Portland. Contact: R. T. Gustafson, MD, 10300 NE Hancock Street, Portland 97220.

INTERNAL MEDICINE

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

November 16—**Peripheral Hyperalimentation Symposium.** Greenwood Inn, Beaverton. Contact: David N. Gilbert, MT, Providence Medical Center, 700 NE 47th Ave., Portland 97213.

November 16—**Circuit Course Program on Infectious Disease.** Salem Memorial Hospital, Salem. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Ave., Portland 97201.

November 17—**Circuit Course Program on Endocrinology.** Albany General Hospital, Albany. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Ave., Portland 97201.

November 19-20—**Pain Problems in Cancer.** Red Lion Motor Inn, Portland. Contact: John E. Stanwood, MD, Emanuel Hospital, 3001 N Gantenbein, Portland 97227.

December 7—**Circuit Course Program on Lower GI.** Presbyterian Intercommunity Hospital, Klamath Falls. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Ave., Portland 97201.

December 8—**Circuit Course Program on Lower GI.** St. Charles Medical Center, Bend. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Ave., Portland 97201.

December 9-10—**Urology for the Non-Urologist.** Oregon Medical Association Headquarters, Portland. Contact: J. S. Reinschmidt, MD, Director of Continuing Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

STATEMENT OF OWNERSHIP, MANAGEMENT AND CIRCULATION as required by the Act of August 12, 1970: Section 3685, Title 39, United States Code for THE WESTERN JOURNAL OF MEDICINE, published monthly at San Francisco, California, for September, 1977.

1. Location of known office of publication: 731 Market Street, San Francisco, California 94103.

2. Location of the headquarters or general business office of the publisher: 731 Market Street, San Francisco, California, 94103.

3. Publisher: California Medical Association, 731 Market Street, San Francisco; Editor, Malcolm S. M. Watts, M.D., 731 Market Street, San Francisco; Managing Editor, David Greer, 731 Market Street, San Francisco.

4. Owner: (If owned by a corporation, its name and address must be stated and also immediately thereunder the names and addresses of stockholders owning or holding 1 percent or more of total amount of stock. If not owned by a corporation, the names and addresses of the individual owners must be given. If owned by a partnership or other unincorporated firm, its name and address, as well as that of each individual must be given.) California Medical Association, 731 Market Street, San Francisco, California 94103 (an unincorporated association).

5. Known bondholders, mortgagees, and other security holders owning or holding 1 percent or more of total amount of bonds, mortgages or other securities. There are no bondholders, mortgagees, or other security holders.

6. Paragraphs 4 and 5 include, in cases where the stockholder or security holder appears upon the books of the company as trustee or in any other fiduciary relation, the name of the person or corporation for whom such trustee is acting, also the statements in the two paragraphs show the affiant's full knowledge and belief as to the circumstances and conditions under which stockholders and security holders who do not appear upon the books of the company as trustees, hold stock and securities in a capacity other than that of a bona fide owner. Names and addresses of individuals who are stockholders of a corporation which itself is a stockholder or holder of bonds, mortgages or other securities of the publishing corporation have been included in paragraphs 4 and 5 when the interests of such individuals are equivalent to 1 percent or more of the total amount of the stock or securities of the publishing corporation.

7. Average number of copies each issue during preceding 12 months: Total, 30,656; paid circulation by mail subscription, 29,432; sales through dealers and carriers, street vendors and counter sales, 0; free distribution (including samples) by mail, carrier or other means, 639; total distribution, 30,071; office use, leftover, unaccounted, spoiled after printing, 584; total net press run, 30,656. Single issue nearest to filing date, September, 1977. Total 32,869; paid circulation by mail subscriptions, 29,974; sales through dealers and carriers, 0; free distribution (including samples) by mail, carrier or other means, 648; total distribution, 30,622; office use, leftover, unaccounted, spoiled after printing, 2,247, total net press run, 32,869. David Greer, Managing Editor.

December 15—**Circuit Course Program on Lower GI.** St. Anthony Hospital, Pendleton. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Ave., Portland 97201.

December 15—**Current Concepts in Exercise Testing and Training in Coronary Heart Disease.** YMCA, Portland. Contact: M. R. Malinow, MD, 505 NW 185th Avenue, Beaverton 97005.

January 5—**Circuit Course Program on Stroke Prevention.** Recreation Cafe, The Dalles. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Ave., Portland 97201.

January 11—**Circuit Course Program on Endocrinology.** Douglas Community Hospital, Roseburg. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Ave., Portland 97201.

January 12—**Circuit Course Program on Endocrinology.** Thunderbird Courtel, Coos Bay. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Ave., Portland 97201.

January 18—**Circuit Course on Stroke Prevention.** Salem Memorial Hospital, Salem. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Ave., Portland 97201.

January 25—**Circuit Course on Stroke Prevention.** Rogue Valley Memorial Hospital, Medford. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Ave., Portland 97201.

January 26—**Circuit Course on Stroke Prevention.** Sacred Heart Hospital, Eugene. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Ave., Portland 97201.

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In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-64, Seattle, Washington 98195. Phone: (206) 543-6995.

November 16—**New Antibiotics, Surgical Antibiotic Prophylaxis—University of Wash. in Anacortes, Wash.** Wednesday, 8-10 a.m., Island Hospital. Contact: Harry Eiesland, MD, 24th St. and "M" Ave., Anacortes, WA 98221. (206) 293-3101.

November 16-18—**Osteoporosis and Metabolic Bone Disease Scanning—Univ. of Wash. Internal Medicine Review Sessions in Montana.** Wednesday, Nov. 16, Great Falls. Contact: Mr. John Breeden, Box 2829, Great Falls, MT 59403. (406) 453-1493. Thursday, Nov. 17, Billings; 7:30-10 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, Nov. 18, Missoula; 8:30-11 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

November 18—**Disorders of the Low Back.** Friday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

November 28-29—**Pulmonary I—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, Nov. 28, Wenatchee; 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, Nov. 29, Yakima; 5-7 p.m., Memorial Hospital. Contact: Harry Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 248-6791.

December 3—**Northwest Urological Society Annual Scientific Meeting.** Saturday. Olympic Hotel, Seattle. Contact: Northwest Urological Society, Suite 405, 801 Broadway, Seattle, 98122.

December 5-6—**Diabetes in Pregnancy. Univ. of Wash. OB-GYN Sessions in Idaho, Washington.** Monday, Dec. 5, Boise. Contact: David M. Barton, MD, 999 North Curtis Rd., Boise, ID 83704. (208) 385-9391. Tuesday, Dec. 6, Spokane. Contact: Wm. Harvey Frazier, MD, 101 West 8th Ave., Spokane, WA 99204. (509) 838-8347.

December 5-8—**Pediatric Oral Surgery. Univ. of Wash. Pediatrics Sessions in Idaho, Montana, Washington.** Monday, Dec. 5, Pocatello. Contact: Robert H. Judd, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443. Tuesday-Wednesday, Dec. 6-7, Spokane. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220. Wednesday-Thursday, Dec. 7-8, Great Falls. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

December 7-9—**Clinical Topics in Internal Medicine.** Wednesday-Friday. Virginia Mason Medical Center Auditorium, Seattle. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101.

December 14-16—**Leukemia, Lymphomas and Advances in Medical Oncology—Univ. of Wash. Internal Medicine Review Sessions in Montana.** Wednesday, Dec. 14, Great Falls. Contact: Mr. John Breeden, Box 2829, Great Falls, MT 59403. Thursday, Dec. 15, Billings. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, Dec. 16, Missoula. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

January 6-7—**Radiology of the Pancreas and Biliary Tract.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1110 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

January 18-20—**Problems in Clinical Endocrinology—American College of Physicians.** Wednesday-Friday. Virginia Mason Medical Center Auditorium, Seattle. Contact: American College of Physicians, 4200 Pine St., Philadelphia, PA 19104. (215) 243-1200.

January 26-28—**The Macula and Fluorescein Angiography—Washington State Academy of Ophthalmology President's Meeting.** Thursday-Saturday. Washington Plaza Hotel, Seattle. 15 hrs. Contact: Charles E. Boylan, MD, 1601 16th Ave., Seattle, WA 98122. (206) 325-8500.

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Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma, in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia), *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

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Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

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Warnings: *Usage in Pregnancy:* The safety of the use of Brethine, brand of terbutaline sulfate, in human pregnancy has not been established. The use of the drug in pregnancy, lactation, or women of childbearing potential requires that the expected therapeutic benefit of the drug be weighed against its possible hazards to the mother or child

Usage in Pediatrics Brethine, brand of terbutaline sulfate, tablets are not presently recommended for children below the age of twelve years due to insufficient clinical data in this pediatric group.

Precautions: Brethine, brand of terbutaline sulfate, should be used with caution in patients with diabetes, hypertension, and hyperthyroidism. As with other sympathomimetic bronchodilator agents, Brethine, brand of terbutaline sulfate, should be administered cautiously to cardiac patients, especially those with associated arrhythmias Although the concomitant use of Brethine, brand of terbutaline sulfate, with other sympathomimetic agents is not recommended, the use of an aerosol bronchodilator of the adrenergic stimulant type for the relief of an acute bronchospasm is not precluded in patients receiving chronic oral Brethine, brand of terbutaline sulfate, therapy

Adverse Reactions: Commonly observed side effects include nervousness and tremor Other reported reactions include headache, increased heart rate, palpitations, drowsiness, nausea, vomiting, and sweating These reactions are generally transient in nature, usually do not require treatment, and appear to diminish in frequency with continued therapy In general, all the side effects observed are characteristic of those commonly seen with sympathomimetic amines

How Supplied: Round, scored, white tablets of 5 mg in bottles of 100 and 1,000 and Unit Dose Packages of 100; oval, scored, white tablets of 2.5 mg in bottles of 100.
(B) 98-146-060-E (Rev 4/76)667004 C76-12

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Division of CIBA-GEIGY Corporation
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Brethine: alone or with theophylline, a second wind for asthmatics.

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Section 79 has been the subject of uncertainty, misinterpretation and unjustified negativism.

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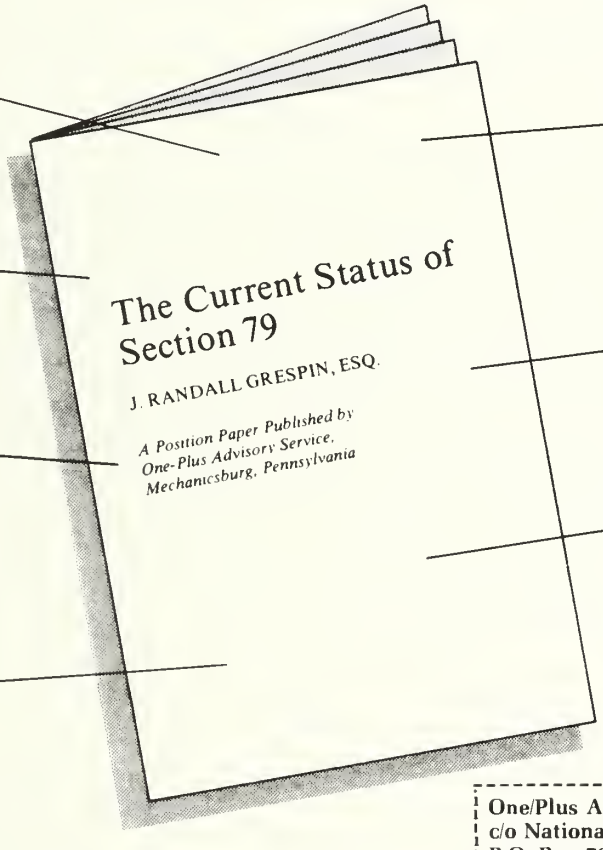

Why the proposed regulations of January 22, 1977 were found unworkable and were withdrawn on March 21, 1977 . . . two months later.

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A New Vision of Catapres® (clonidine HCl)

20/20

The first 20 days

- Catapres lowers blood pressure promptly.
- No contraindications.
- Some patients may have dry mouth, drowsiness, and sedation. Tell them that these tend to diminish with continued use.
- Giving the larger part of the divided dose at bedtime can help alleviate drowsiness and sedation.

The next 20 years*

- Lowered blood pressure.
- Little impotence, depression or postural hypotension.
- No fatal hepatotoxicity in over a decade of worldwide use.
- Broad therapeutic dosage range to keep step with changing dosage needs over the years.

*Tolerance may develop in some patients, necessitating a reevaluation of therapy.

For full details on adverse reactions, warnings, and precautions, see brief summary of the prescribing information on last page of this advertisement.

Catapres® (clonidine HCl)
For Step 2 in
Hypertension

HYPERTENSION

A New Vision of Catapres® (clonidine HCl)

Tablets of 0.1 and 0.2 mg

What you do the first 20 days Can help him the next 20 years

Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potenc It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings ir animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetu
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consultin their physician. Rare instances of hypertensive enceph lopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pres sure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machiner or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any oth agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone, and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and menta depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000.

For complete details, please see full prescribing information.

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Tablets

Percodan® CII

DESCRIPTION Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (WARNING: May be habit forming), 0.38 mg. oxycodone terephthalate (WARNING: May be habit forming), 224 mg. aspirin, 160 mg phenacetin, and 32 mg. caffeine.

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCODAN®, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCODAN® is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCODAN® should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCODAN® may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCODAN® should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCODAN® should not be administered to children.

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCODAN® or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCODAN® should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCODAN® may be additive with that of other CNS depressants. See WARNINGS.

DEA Order Form Required.

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Manati, Puerto Rico 00701
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November 1977 EDO 149P

CONSIDERATIONS FOR ORAL NARCOTIC ANALGESIC USE:

1. Determine need

What is causing pain? How is it perceived by you and your patient?

2. Prescribe a rapid-acting agent

Select a readily-absorbed oral agent that usually acts within 15 to 30 minutes.

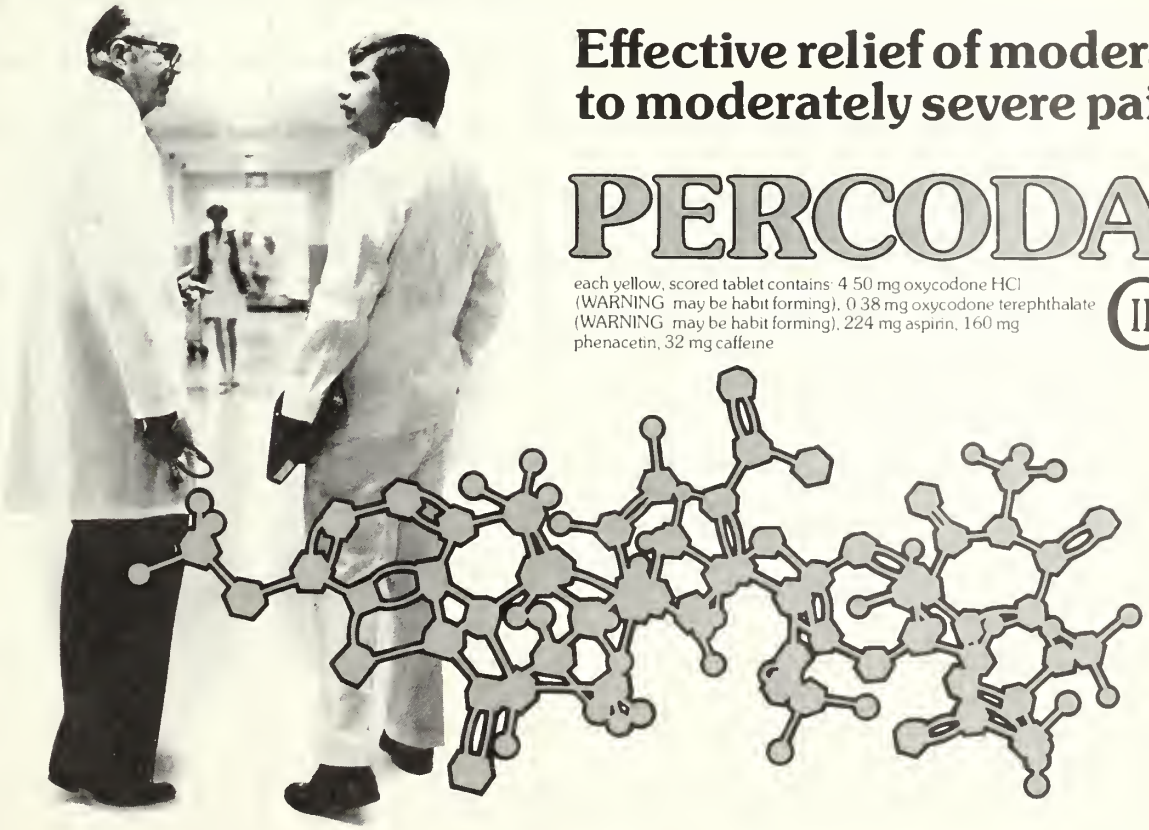
3. Minimize potential risk

Prescribe in limited quantities for selected patients.

Schedule II classification means no refills, no telephone Rx. Patients with persistent pain must return for your evaluation of analgesic needs.

4. Provide adequate analgesia with minimum doses

Consider PERCODAN® because patients rarely ask for increased dosage. PERCODAN® relief can last up to six hours–until time for next tablet.



Effective relief of moderate to moderately severe pain

Tablets

PERCODAN®

each yellow, scored tablet contains: 4.50 mg oxycodone HCl (WARNING may be habit forming), 0.38 mg oxycodone terephthalate (WARNING may be habit forming), 224 mg aspirin, 160 mg phenacetin, 32 mg caffeine

CII

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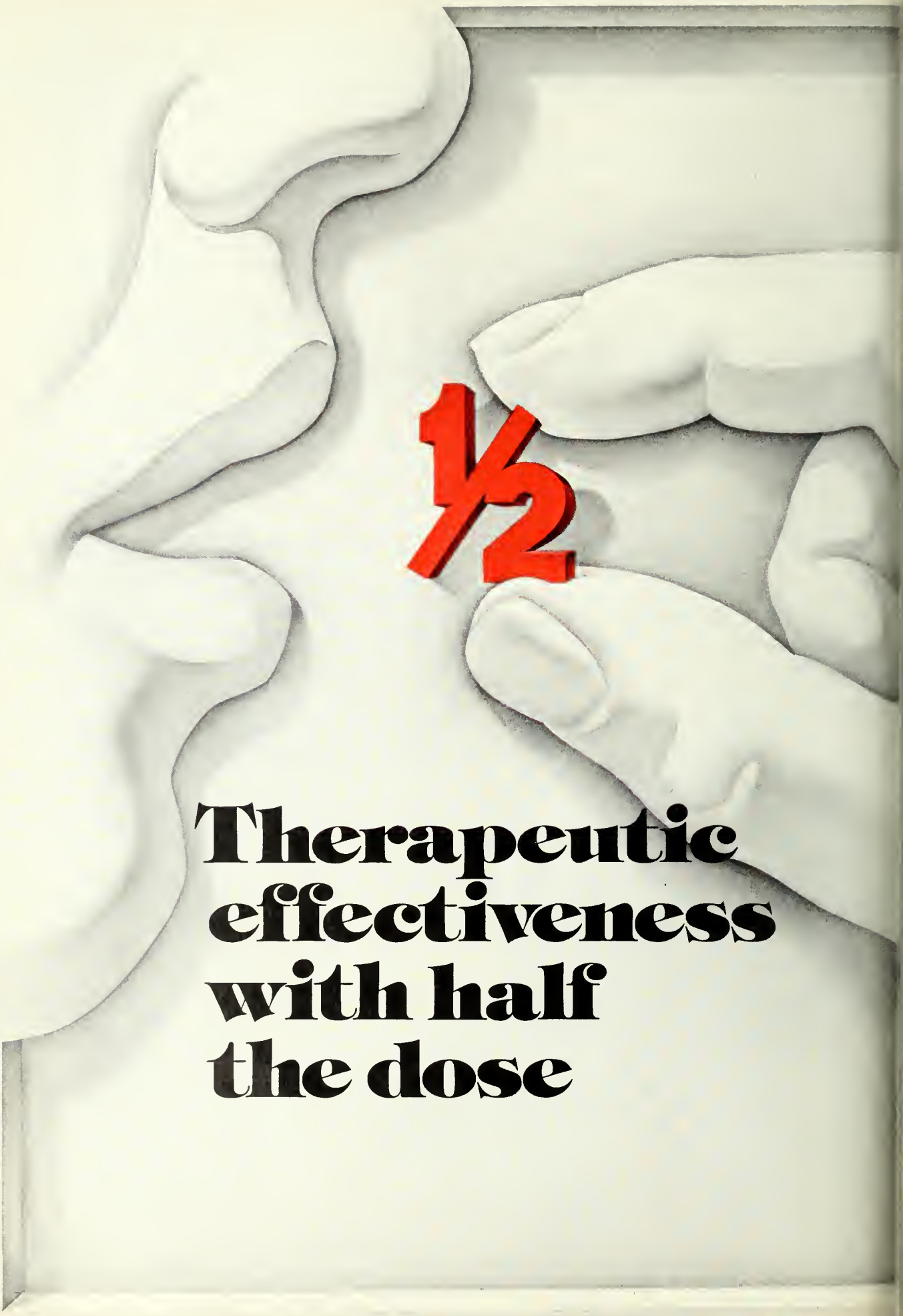
Please see facing page for Brief Summary of prescribing information.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Schering

Once-a-day dosage

Fulvicin® P/G*

brand of
griseofulvin [ultramicrosize], USP
(specially processed) **125 mg. tablets**

*"P/G" means a new polyethylene glycol system for enhanced absorption –

A 250 mg. daily dose (two 125 mg. tablets) of new FULVICIN P/G can replace 500 mg. of griseofulvin (microsize), USP. This is made possible by a special process in which the ultramicrosize griseofulvin crystals are partly dissolved in polyethylene glycol and dispersed through the tablet matrix for enhanced absorption.

Patient convenience –

FULVICIN P/G can be prescribed as two 125 mg. tablets once a day. Compliance is further assured by the easy-to-swallow size of the tablets.

Patient savings –

FULVICIN P/G is up to 35 per cent less expensive per dose than all microsize griseofulvin formulations.**

**Based on list-price comparison.

See Clinical Considerations section on following page...

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Schering

Fulvicin® P/G

brand of griseofulvin [ultramicrosize], USP

(specially processed) **125 mg. tablets**

Clinical Considerations: INDICATIONS FULVICIN P/G Tablets are indicated for the treatment of ringworm infections of the skin, hair, and nails, namely: tinea corporis, tinea pedis, tinea cruris, tinea barbae, tinea capitis, tinea unguium (onychomycosis) when caused by one or more of the following genera of fungi: *Trichophyton rubrum*, *Trichophyton tonsurans*, *Trichophyton mentagrophytes*, *Trichophyton interdigitalis*, *Trichophyton verrucosum*, *Trichophyton megnini*, *Trichophyton gallinae*, *Trichophyton crateriform*, *Trichophyton sulphureum*, *Trichophyton schoenleini*, *Microsporum audouini*, *Microsporum canis*, *Microsporum gypseum*, and *Epidermophyton floccosum*.

Note Prior to therapy, the type of fungi responsible for the infection should be identified.

The use of this drug is not justified in minor or trivial infections which will respond to topical agents alone.

Griseofulvin is not effective in the following: Bacterial infections, Candidiasis (Moniliasis), Histoplasmosis, Actinomycosis, Sporotrichosis, Chromoblastomycosis, Coccidioidomycosis, North American Blastomycosis, Cryptococcosis (Torulosis), Tinea versicolor, and Nocardiosis.

CONTRAINDICATIONS This drug is contraindicated in patients with porphyria, hepatocellular failure, and in individuals with a history of hypersensitivity to griseofulvin.

WARNINGS *Prophylactic Usage* Safety and efficacy of griseofulvin for prophylaxis of fungal infections have not been established.

Animal Toxicology Chronic feeding of griseofulvin, at levels ranging from 0.5-2.5% of the diet, resulted in the development of liver tumors in several strains of mice, particularly in males. Smaller particle sizes result in an enhanced effect. Lower oral dosage levels have not been tested. Subcutaneous administration of relatively small doses of griseofulvin once a week during the first three weeks of life has also been reported to induce hepatomata in mice. Although studies in other animal species have not yielded evidence of tumorogenicity, these studies were not of adequate design to form a basis for conclusions in this regard

In subacute toxicity studies, orally administered griseofulvin produced hepatocellular necrosis in mice, but this has not been seen in other species. Disturbances in porphyrin metabolism have been reported in griseofulvin-treated laboratory animals. Griseofulvin has been reported to have a colchicine-like effect on mitosis and cocarcinogenicity with methylcholanthrene in cutaneous tumor induction in laboratory animals.

Usage in Pregnancy The safety of this drug during pregnancy has not been established.

Animal Reproduction Studies. It has been reported in the literature that griseofulvin was found to be embryotoxic and teratogenic on oral administration to pregnant rats. Pups with abnormalities have been reported in the litters of a few bitches treated with griseofulvin. Additional animal reproduction studies are in progress.

Suppression of spermatogenesis has been reported to occur in rats, but investigation in man failed to confirm this.

PRECAUTIONS Patients on prolonged therapy with any potent medication should be under close observation. Periodic monitoring of organ system function, including renal, hepatic, and hematopoietic, should be done

Since griseofulvin is derived from species of penicillin, the possibility of cross sensitivity with penicillin exists, however, known penicillin-sensitive patients have been treated without difficulty.

Since a photosensitivity reaction is occasionally associated with griseofulvin therapy, patients should be warned to avoid exposure to intense natural or artificial sunlight. Should a photosensitivity reaction occur, lupus erythematosus may be aggravated

Griseofulvin decreases the activity of warfarin-type anticoagulants so that patients receiving these drugs concomitantly may require dosage adjustment of the anticoagulant during and after griseofulvin therapy

Barbiturates usually depress griseofulvin activity, and concomitant administration may require a dosage adjustment of the antifungal agent.

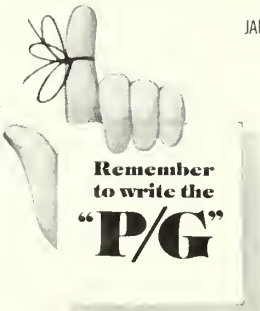
ADVERSE REACTIONS When adverse reactions occur, they are most commonly of the hypersensitivity type, such as skin rashes, urticaria, and rarely, angioneurotic edema, and may necessitate withdrawal of therapy and appropriate countermeasures. Paresthesias of the hands and feet have been reported rarely after extended therapy. Other side effects reported occasionally are oral thrush, nausea, vomiting, epigastric distress, diarrhea, headache, fatigue, dizziness, insomnia, mental confusion, and impairment of performance of routine activities.

Proteinuria and leukopenia have been reported rarely Administration of the drug should be discontinued if granulocytopenia occurs.

When rare, serious reactions occur with griseofulvin, they are usually associated with high dosages, long periods of therapy, or both.

10705231 JANUARY 1977

For more complete details, consult package insert or Schering literature available from your Schering Representative or Professional Services Department, Schering Corporation, Kenilworth, New Jersey 07033.



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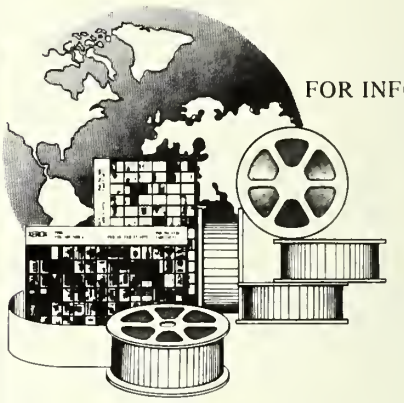

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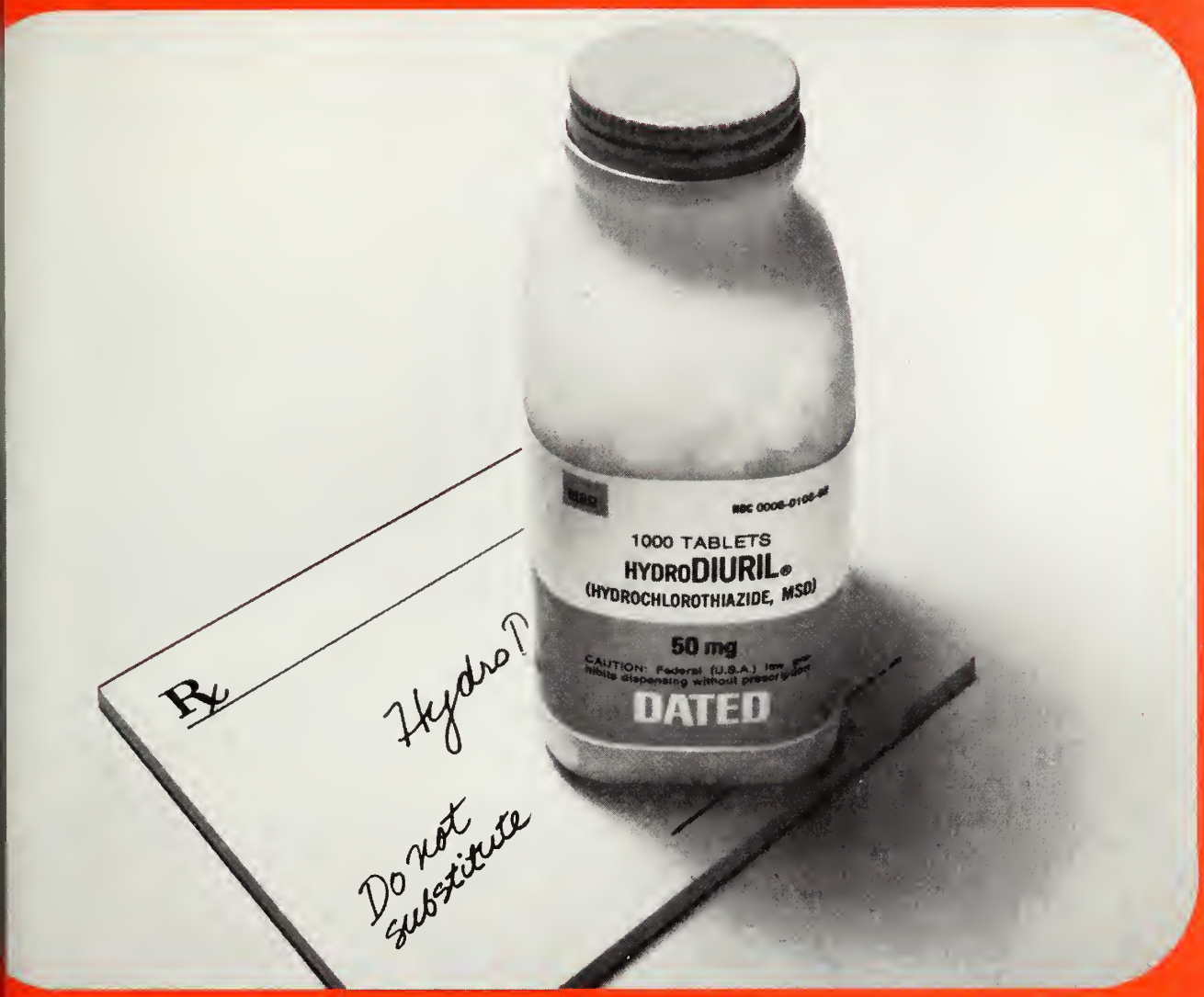
Contraindications: Anuria; hypersensitivity to this or other sulfonamide-derived drugs.
Warnings: Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read circulars for lithium preparations before use of such concomitant therapy.
Use in Pregnancy: Thiazides cross placental barrier and appear in cord blood; in pregnancy, weigh anticipated benefit against possible hazards to fetus, including fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.
Nursing Mothers: Thiazides appear in breast milk; if use of drug is deemed essential, patient should stop nursing.
Precautions: Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis in severe cirrhosis, with concomitant corticosteroid or ACTH therapy, with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.
Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in post-sympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal im

or experience—



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ent becomes evident, consider withholding or discontinuing c therapy. Thiazides may decrease serum PBI levels without of thyroid disturbance. Calcium excretion is decreased by des. Pathologic changes in the parathyroid gland with hyper- mia and hypophosphatemia have been observed in a few patients llonged therapy; thiazides should be discontinued before testing rathyroid function.

rse Reactions: *Gastrointestinal System*—Anorexia; gastric ir- n; nausea; vomiting; cramping; diarrhea; constipation; jaundice epatic cholestatic jaundice); pancreatitis; sialadenitis.

al Nervous System—Dizziness; vertigo; paresthesias; headache; opsia.

tologic—Leukopenia; agranulocytosis; thrombocytopenia; ic anemia.

ovascular—Orthostatic hypotension (may be aggravated by l, barbiturates, or narcotics).

sensitivity—Purpura; photosensitivity; rash; urticaria; necrotizing s (vasculitis) (cutaneous vasculitis); fever; respiratory distress ing pneumonitis; anaphylactic reactions.

—Hyperglycemia; glycosuria; hyperuricemia; muscle spasm; ness; restlessness; transient blurred vision.

ever adverse reactions are moderate or severe, thiazide dosage be reduced or therapy withdrawn.

: When used with other antihypertensive drugs, careful observa- or changes in blood pressure must be made, especially during therapy. Dosage of other antihypertensive agents must be reduced by at least 50 percent as soon as this drug is added to the regimen. As blood pressure falls under the potentiating effect of this agent, further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary.

How Supplied: Tablets containing 25 mg hydrochlorothiazide each in bottles of 100 and 1000 and single-unit packages of 100; Tablets containing 50 mg hydrochlorothiazide each in bottles of 100, 1000, and 5000 and single-unit packages of 100; Tablets containing 100 mg hydrochlorothiazide each in bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

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THE DEPARTMENT OF FAMILY PRACTICE, UCLA School of Medicine, seeks an Associate physician for the Department of Family Practice at Kern Medical Center, its affiliate in Bakersfield, California. Board certification or eligibility in Family Practice or Internal Medicine required. Salary competitive, with full medical liability coverage. Interested candidates should direct inquiries, credentials, and curriculum vitae to Ramon H. Neufeld, MD, MPH, Chairman, Department of Family Practice, Kern Medical Center, 1830 Flower Street, Bakersfield, California 93305. Telephone (805) 323-7651. Both the University of California and Kern Medical Center are equal opportunity employers.

BUSY CENTRAL CALIFORNIA COAST OPHTHALMOLOGIST wants associate immediately. Send résumé. Write P.O. Box 309, Monterey, CA 93940.

SAN FRANCISCO: INTERNIST OR MEDICAL SUB-SPECIALIST wanted to share downtown San Francisco GENERAL INTERNAL MEDICINE PRACTICE located across from major hospital. Position available about January 1, 1978. Contact: Darryl L. Raszl, MD, 909 Hyde St. Suite 432, San Francisco, CA 94109.

OB-GYN—We are seeking a Board Certified or eligible physician to replace an OB partner lost because of health reasons. We are a 20 physician, multi-specialty group located 55 miles northwest of Chicago in the Chain-O-Lakes resort area with easy access to the city. Our candidate will step into an active three man OB-GYN practice with incentive pay from day one (with a guaranteed minimum draw), malpractice paid, excellent fringe benefits. Our group is physically adjacent to a 144 bed general community hospital and State Trauma Center. Call or write Jim Dickson, McHenry Medical Group, 1110 North Green Street, McHenry, Illinois 60050 - 815/385-1050.

STAFF INTERNIST—PHOENIX, ARIZONA—Board eligible or certified in Internal Medicine, responsible for some diagnostic examinations, executive physical examinations, and counseling. Salary competitive with liberal benefits. An Affirmative Action/Equal Opportunity employer. Submit résumé to Box 5959, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

RESEARCH SURGEONS, SURGICAL ONCOLOGY—The Division of Oncology, Department of Surgery, UCLA School of Medicine, has a position open for an Assistant Professor of Surgery. Experience in cancer surgery, tumor immunology and chemotherapy preferred. Salary negotiable. An affirmative action employer. Applications from women and minority groups encouraged. Please direct inquiries to Donald L. Morton, MD, Chief, Division of Oncology, Department of Surgery, UCLA School of Medicine, Los Angeles, CA 90024.

GENERAL PRACTITIONER for busy group in East Los Angeles. Full time. Spanish speaking helpful. No night or weekend calls; no OB or hospital work. Excellent salary and paid malpractice. MD or DO, Phone (213) 269-0421.

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(214) 358-5611

FAMILY PRACTITIONER needed for a position wtih a young and aggressive group practice. Current opening exists due to acquisition of new clinic office. Send résumé to: William F. Miller, Administrator, Valley West General Hospital, 300 De Soto Drive, Los Gatos, CA 95030; (408) 356-4111.

THE CALIFORNIA HEALTH SERVICES CORPS has opportunities for primary care physicians in mountain, desert and agricultural areas of California. Malpractice coverage is provided in addition to state equivalent salary and benefits. Contact Rural Health Section, State Department of Health, 714 "P" Street, Room 476, Sacramento, Ca. 95814. (916) 322-4704.

FP's for fresh approach to Primary Care. Group practice with independent freedom. All administration eliminated. No financial risks. Hospital-based or associate practices in several pleasant N. California communities. FFS with $40,000 annual guarantee. Minimal night-call. E.R. back-up available. CONTACT: EMS, 2310 Mason St., San Francisco, CA 94133. (415) 956-5900.

CALIFORNIA, Monterey: Full-time career-oriented emergency physician wanted to join established ED group in small-size full service nonprofit hospital. Fee for service (with guaranteed minimum) malpractice insurance paid, flexible schedule. Send CV to or call: Saul Kunitz, MD, Eskaton Monterey Hospital, P.O. Box 431, Monterey, CA 93940, (408) 375-2621.

CHIEF PSYCHIATRIST to join a County Mental Health Services Program located in the Central Valley and 120 miles from the San Francisco Bay area. Salary $47,930 plus liberal fringe benefits—one year of experience as a Psychiatrist and Board Certified. Contact: Dr. Dale Wolff, Director of Mental Health Services, 480 East 13th Street, Merced, CA 95340. Phone: (209) 723-8861.

GENERAL PRACTITIONER wanting a permanent job as company doctor in lumber related firm. Work would entail primarily physicals and filing medical claims for insurance purposes. Eight hours a day, five days a week. Insurance coverage provided. Write P.O. Box 670, Turlock, California 95380.

(Continued on Page 22)

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(Continued from Page 20)

PHYSICIANS WANTED

CHAIRPERSON, DEPARTMENT OF SURGERY—The University of California, Davis, is seeking the most highly qualified individual to become Chairperson of its Department of Surgery on January 1, 1978. Candidates must be at the associate or full professor level and have substantial background in academic surgery, with interest and experience in patient care, teaching, research, and administration. UCD is an Equal Opportunity-Affirmative Action Employer. Interested persons should submit letters summarizing their qualifications and Curriculum Vitae at the earliest possible time to Paul R. Lipscomb, MD, Chairperson, Search Committee, UCD Professional Building, 4301 X Street, Sacramento, CA 95817.

INTERNIST NEEDED for multispecialty group. Excellent working conditions, fringe benefits, salary and bonus dependent on individual effort. Excellent medical community. Maintenance of individuality within the corporate structure stressed. Interested parties contact F. E. Roque, MD, Fresno Medical Group, Inc., 1300 N. Fresno St., Fresno, CA 93703. Phone (209) 486-3610.

CALIFORNIA, Santa Clara County: Experienced, career-oriented emergency physicians wanted to join well established group. Fee-for-service compensation. Position available immediately. Please direct inquiries with curriculum vitae to Associated Emergency Physicians, Inc., 1530 The Alameda, No. 28, San Jose, CA 95126 or phone: (408) 956-5900.

50-MAN MULTISPECIALTY CLINIC seeks General Surgeon, Board Certified or eligible, to fill out active department located in pleasant coastal city. Contact Box No. 5960, Western Journal of Medicine, 731 Market Street, San Francisco, CA 94103.

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PHYSICIANS
Career Opportunities Available

Major midwestern teaching and research medical center has career opportunities for the specialties listed below. These appointments afford the benefit of practicing as a member of a "closed staff" group practice, with representatives from 39 medical specialties. Facilities include a 1,100-bed teaching hospital with a large outpatient clinic and three suburban satellite clinics. Major medical school affiliations afford additional teaching opportunities.

Individual based salary, commensurate with experience and comprehensive benefits are offered. These include: malpractice insurance, retirement plan, BC/BS Master Medical, life, accident, travel and dental insurance coverage, as well as a lease car plan and many extras.

ALLERGIST—Board Certified or Board Eligible—Appointment would encompass activities at our central campus and our newly established suburban clinics.

ANESTHESIOLOGIST—Director of Education—Board Certified anesthesiologist with experience in residency training programs. A qualified individual will be given the responsibility to reinstate and direct a three year residency program in anesthesiology.

CARDIOLOGIST—Board Certified or Board Eligible—Seeking individual trained in Coronary Care, Noninvasive Cardiology and Rehabilitation Cardiology to participate in an active clinical research and teaching program.

EMERGENCY MEDICINE—Board Certified or Board Eligible physicians and general surgeons for positions in our Emergency Medicine Division.

GASTROENTEROLOGIST—Board Certified gastroenterologist with special interest in gastrointestinal cancer.

GENERAL INTERNIST—Board Certified Internist for position in the Department of Medicine at central campus and a position for a Board Certified or Board Eligible General Internist at one of our suburban satellite clinics.

GENERAL SURGEON—Board Certified with 5-10 years experience, interested in either (1) general surgery, (2) intensive care, (3) head and neck, or (4) research as their area for concentration.

NEUROSURGEON—Board Certified or Board Eligible for a position in the Department of Neurosurgical Surgery.

ORTHOPEDIC SURGEON—Board Certified or Board Eligible—The appointment would encompass activities at central campus and newly established suburban clinics. Position entails major surgery and participation in teaching at the central campus as well as outpatient practice and minor surgical procedures performed at the suburban clinics.

OTOLARYNGOLOGIST—Board Certified or Board Eligible. Appointment would encompass activities at our central campus and newly established suburban clinics. Position entails surgery and participation in teaching at the central campus as well as outpatient practice and minor surgical procedures performed at the suburban clinics.

PSYCHIATRIST—Board Certified or Board Eligible—Instructorships available with major universities, positions available at main campus as well as suburban centers. Areas of concentration for interested individuals should lie in either (1) clinical outpatient, (2) liaison consulting, (3) crisis intervention.

RADIOLOGIST—Board Certified general diagnostic radiologist and an angiography specialist for main campus, suburban centers as well as major affiliate medical schools. The Department of Diagnostic Radiology is multi-facet in that it is composed of individual "centers" for general diagnostic activities, nuclear medicine activities, ultrasound activities, and most recently, computed tomograph procedure which includes both EMI head and EMI body scanner. The training program includes an accredited Residency Program and allied Health Science Education Program in the area of Nuclear Medicine, Radiologic Technology, and Ultrasound Technology.

THERAPEUTIC RADIOLOGIST—Board Certified or Board Eligible Therapeutic Radiologist for position in the Department of Therapeutic Radiology.

Interested parties should send their curriculum vitae in strict confidence. Write BOX NO. 5949, WESTERN JOURNAL OF MEDICINE, 731 MARKET ST., SAN FRANCISCO, CA 94103.

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All communities have modern JCAH accredited hospitals and a recognized need for additional physicians. If you are interested in a challenging practice and pleasant surroundings, please write us and include your curriculum vitae, starting availability date, geographical preference, type of practice, and size of community desired.

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a National Hospital Management Company has a number of communities in need of physicians. We have several types of practice opportunities available in California, Virginia, Alabama, Illinois and Mississippi. One such opportunity exists for an internist in Southern California. Located 75 Miles south of Los Angeles, this vital community offers proximity to both the coast and mountains/ski area, with excellent schools, churches, recreational and cultural activities. Guaranteed first year income, office space and household move is paid. If you would like a really rewarding practice in an area where you are needed and appreciated please send curriculum vitae to: **JOE ANN LINDSEY, QUALICARE, INC., P.O. Box 24189, New Orleans, LA 70184 or call collect at (504) 837-6456.**

Assistant Professor of Surgery/Otolaryngology

University of California at San Diego

Qualifications include: (1) Eligible for certification of the American Board of Otolaryngology; (2) Medical licensure in California; (3) Surgical skills in all aspects of head and neck surgery; (4) Experience and skill in teaching at undergraduate and postgraduate levels; (5) Knowledge and skill in basic research in otolaryngology; (6) Experience and skill in administration in an academic environment.

Salary commensurate with the rank and step of appointment within the established salary schedule of University of California, San Diego.

Contact:
Alan M. Nahum, MD
Head, Division of Otolaryngology
University Hospital
225 W. Dickinson Street
San Diego, CA 92103

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PHYSICIANS WANTED

TEACHING POSITION FOR EXPERIENCED FAMILY PHYSICIAN—Position available as director of the Williamsburg Family Practice Office, a teaching practice, affiliated with the Department of Family Pracice, University of Iowa. American Board of Family Practice certification required. Prosperous farming community, practice serves 6,000 people. New office building. 25 miles from University Medical Center. Faculty appointment with salary and University fringe benefis, including malpractice insurance. University community offers excellent cultural and educational opportunities. Night and weekend coverage will be shared by residents. Direct inquiries to: Robert E. Rakel, MD, Professor and Head, Department of Family Practice, University of Iowa College of Medicine, Iowa City, Iowa 52242.

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The Pondera Medical-Dental Clinic is currently recruiting four associates to form the nucleus of a new concept in rural health care delivery. We are looking for the following physicians to add to our current staff of three general practitioners and a board cerified radiologist:

(a) General Practitioner
(b) General Surgeon
(c) Internist
(d) Urologist

The new clinic is associated with Pondera Hospital, a modern acute care facility fully accredited by the JCAH, providing a complete range of services.

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Bristol Messer, Administrator
Pondera Medical-Dental Clinic
P.O. Box 757
Conrad, Montana 59425

PHYSICIAN NEEDED

A relaxing atmosphere but rewarding challenge for 2 G.P.'s preferably surgery and OB experience, is waiting for you. All outdoor activities and sports are available for all seasons, cultural arts are within 40 miles. A medical school and continuing education is closeby and available. The hospital has 31 beds with 3 G.P.'s on staff. A doctors clinic is available immediately adjacent to the hospital plus other locations.

Please send CV or call collect:

(801) 623-1242
David Peterson, Administrator
Juab County Hospital
Nephi, Utah 84648

GASTROENTEROLOGIST (Clinical Hepatologist)—Major midwestern teaching and research medical center has a career opportunity for a Board Certified Gastroenterologist with expertise in clinical hepatology. Research opportunities will be available for a qualified candidate. The appointment affords the benefits of practicing as a member of a "closed staff" group practice with major facilities which include a 1,100-bed teaching hospital and 39 medical specialties located at our main campus and three suburban satellite clinics. Affiliation with major medical universities affords additional teaching opportunities. Salary and fringe benefits are competitive and the latter includes: malpractice insurance, generous vacation and travel time, a sound disability insurance, as well as life insurance, a tax sheltered annuity, a low cost lease car plan along with many other benefits. Interested physicians should forward their curriculum vitae in strict confidence. Reply Box No. 5962, Western Journal of Medicine, 731 Market Street, San Francisco, CA 94103.

THERAPEUTIC RADIOLOGIST—Major midwestern teaching and research medical center has an opportunity available for a Rediation Therapist in its Department of Therapeutic Radiology. The appointment affords the benefits of practicing as a member of a "closed staff" group practice with major facilities which include an 1,100-bed teaching hospital and 39 medical specialties located at our main campus and three suburban satellite clinics. Affiliation with major medical universities affords additonal teachng opportunities. The Department of Therapeutic Radiology is presently composed of three (3) staff physicians; three (3) residents in an approved Residency Program; eight (8) technologists, seven (7) of whom are registered in therapy; one (1) physicist; one (1) research assistant; one (1) nurse; and an 8-member clerical pool. Teaching involves other staff physicians, residents, 3rd and 4th year medical students, and radiation therapy technology students. Equipment includes a Clinac-12 Accelerator; 35 MEV Brown Boveri Betatron; stationary and rotational Cobalt; simulator and transverse tomography; afterloading interstitial and intracavitary; computer dosimetry; and mould room. The Department treats 900 new and recurrent cases every year. Excellent cooperation between the Therapeutic Radiology Department and other medical and surgical departments affords opportunities to treat patients with diversity of malignant diagnoses, in a multidisciplinary setting. We are in the position to offer an excellent individually based salary commensurate with experience, and a comprehensive benefit program. Interested physicians should forward their curriculum vitae in strict confidence. Reply Box 5963, Western Journal of Medicine, 731 Market Street, San Francisco, CA 94103.

CERTIFIED FAMILY PRACTITIONER AND EXPERIENCED FULL-TIME EMERGENCY PHYSICIANS with California license, needed to join new Diagnostic & Treatment Center in Glendale (Los Angeles area). Salary $48,000/year with annual raise/bonus to $71,500 by 5th year. Liability insurance. Incentive benefits. Contact John Lima, MD, Medical Director, Glendale Community Diagnostic & Treatment Center, 801 So. Chevy Chase, Glendale, CA 91205. (213) 244-4692.

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PHYSICIANS WANTED

GERIATRICIAN—Physician experienced in geriatrics and geriatric programs; to design and implement inpatient and outpatient geriatrics program; participate in approved internal medicine and surgery residency training programs; provide direct patient care. Send résumé to Russell D. Tyler, MD, Medical Director, Health Care Services, Santa Barbara General Hospital, P.O. Box 3650, Santa Barbara, CA 93105.

MENDOCINO COUNTY: Three pediatricians and two nurse practitioners from diverse backgrounds seek a fourth pediatrician for rural, family-centered practice which encourages innovation and individual expression. Close ties with UCSF, UC Irvine. Call (707) 485-7691. Pomo Medical Group, P.O. Box 879, Ukiah, CA 95482.

BOARD CERTIFIED OR ELIGIBLE—General Internist, Oncologist needed for 45-man multispecialty group. Adjacent 400-bed community hospital. Excellent location, San Francisco Bay Area. University teaching affiliations available. Contact Administration, The San Jose Medical Clinic, 45 So. 17th Street, San Jose, CA 95112. Phone (408) 998-5551.

(Continued on Page 24)

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(Continued from Page 23)

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THE DEPARTMENT OF OBSTETRICS AND GYNECOLOGY, Kern Medical Center, Bakersfield, California, is seeking a fulltime Associate in Obstetrics and Gynecology. The Department is an affiliate of the University of California at Los Angeles. The qualifications for the candidate should include (1) certification by the American Board of Obstetrics and Gynecology, (2) California licensure, and (3) interest and skill in teaching resident physicians and medical students. Highly preferred is interest and/or training in maternal and child welfare. Compensation is competitive. Interested candidates should direct their inquiries and curriculum vitae to Leroy E. Smale, MD, Chairman, Department of Obstetrics and Gynecology, Kern Medical Center, 1830 Flower Street, Bakersfield, CA 93305; telephone (805) 323-7651. Both the University of California and Kern County are Equal Opportunity/Affirmative Action Employers.

DELIGHTFUL COLORADO RURAL COMMUNITY seeks compatible medical group to render primary care in any or all specialties. Excellent recreational opportunities nearby. Contact, Administrator, Prowers Medical Center, Lamar, CO 81052.

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OPHTHALMOLOGIST SEEKING PART-TIME POSITION IN SAN DIEGO AREA to supplement academic income. ABO Certified. Top residency and fellowship. Expert fluorescein angio. Box No. 5961, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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GEORGE McGOVERN, U.S. Senate; DENIS BURKITT, MD; LOUIS JUNKER, PhD, Department of Economics, Western Michigan University, Kalamazoo.

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DAVID ABBEY, PhD, Associate Director, Survey Research Science, Loma Linda; HANS A. DIEHL, Doctor of Health Science, Research Director, with DON MANNERBERG, MD, Medical Director, and LESLIE CERA, MD, FRCP(C), FACP, LRI Staff.

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JAMES W. ANDERSON, MD, Associate Professor, University of Kentucky Medical Center, Lexington, KY.

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HUGH TROWELL, MD, formerly Consultant Physician, Department of Medicine and Pediatrics, Makere University and Uganda Government.

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CLOFIBRATE. JOE D. GOLDSTRITCH, MD, FACC, LRI Staff.
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Creatine Phosphokinase-MB (CPK-MB) and the Diagnosis of Myocardial Infarction

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Creatine phosphokinase-MB (CPK-MB) is the most sensitive and the most specific indicator available for the diagnosis of an acute myocardial infarction. With the exception of after-cardiac surgical procedures, the degree and the duration of CPK-MB elevation in serum approximates the extent of an acute myocardial infarction, although a variety of factors may affect the reliability of such an index. Differences in the fractionation and assay methods for the creatine phosphokinase isoenzymes have produced conflicting documentation as to the presence of CPK-MB in tissues other than myocardium and the release of CPK-MB under conditions other than an acute myocardial infarction. The embryological development of the CPK-MB isoenzymes, as well as the various conditions involving increased CPK-BB serum activity, also deserve attention.

THE DIAGNOSIS of myocardial infarction (MI) has been classically based on a history of chest pain plus electrocardiographic (ECG) documentation of new Q-waves and evolving ST-T wave changes. Misdiagnosis is known to occur, for some patients either describe atypical symptoms or suffer a so-called "silent MI."[1,2] Moreover, a significant number of false-positive[3] and false-negative[4] results have been reported on ECG. Even clinical correlation with autopsy findings may produce biased results, since some 6 to 12 hours may be required after the onset of chest pain before the distinctive changes of myocardial necrosis can be detected at postmortem examination. As a result, clinical laboratories have become increasingly relied upon either to establish or to rule out the diagnosis of acute myocardial infarction. Since Wroblewski and co-workers first reported the association of elevated serum glutamic oxaloacetic transaminase (SGOT) activity with the occurrence of an acute MI,[5] a number of enzymes have been found to exhibit increased serum levels during the course of an acute MI. The enzymes, SGOT, lactic dehydrogenase (LDH), and creatine phosphokinase (CPK), are measured most frequently, but they are present in a variety of tissues and are released into serum under a variety of circumstances other than myocardial infarction.[6,7] The search for specific myocardial markers has led to improved techniques for the quantitative analysis of the isoenzymes of LDH and CPK. Despite great enthusiasm for the isoenzyme CPK-MB as a diagnostic indicator of myocardial infarction, the current medical literature contains conflicting reports as to whether: (1) CPK-MB is present only in myocardium, (2) CPK-MB is released only with myocardial infarction and (3) the degree and duration of CPK-MB elevation in serum reflects the extent of myocardial infarction.

Some of the discrepancies in the reports of CPK-MB activity arise from pronounced differences in either fractionation or assay techniques. At least three CPK isoenzymes, MM, MB and BB, have been separated either by electrophoresis or

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ABBREVIATIONS USED IN TEXT

ATP = adenosine triphosphate
CCU = coronary care unit
CPK = creatine phosphokinase
ECG = electrocardiogram (electrocardiographic)
LDH = lactic dehydrogenase
MI = myocardial infarction
NADPH = dihydronicotinamide adenine dinucleotide phosphate
SGOT = serum glutamic oxaloacetic transaminase

column chromatography (see Figure 1). Other minor bands of CPK activity,[8-12] including a mitochondrial enzyme,[13,14] have been identified, but their clinical significance remains obscure. Assay of CPK activity usually is conducted by using a coupled enzyme system, involving hexokinase and glucose-6-phosphate dehydrogenase, and linking the production of adenosine triphosphate (ATP) in the reverse CPK reaction to the ultimate formation of dihydronicotinamide adenine dinucleotide phosphate (NADPH) (see Figure 2). The NADPH is then measured by spectrophotometry or fluorometry, or by the formation of an insoluble dye, such as formazan. The CPK isoenzymes readily lose their activity unless some thiol compound is added to the assay media.[15] Moreover, a number of anions reversibly inactivate CPK-BB[18] and heat can irreversibly inactivate all the CPK isoenzymes.[19] Dilution of serum samples can result in enhanced CPK activity, although the ratio of activities for the CPK isoenzymes remains constant.[20] Thus the final reported activities for the CPK isoenzymes separated either by electrophoresis or column chromatography may differ depending not only on the temperature, pH or buffer employed, but also on the nature and concentration of thiol reagent used, the penetration of the coupled indicator enzymes into the support gels, or the extent of isoenzyme elution from the support gels.[6,21,22] An assay method based on the differential thiol activation of CPK-MM and CPK-MB by glutathione and dithiothreitol has been reported,[23,24] but subsequent workers have found it to be unreliable.[25-30] Also, an immunological technique, utilizing antibodies to either the M- or B-subunit of CPK, has been applied quantitatively in a research setting,[31] but its routine clinical utility remains to be established.

The CPK isoenzymes MM, MB and BB are present primarily in the cytosol,[32] but have also been reported associated with the myofibrillar apparatus of muscle cells.[33,34] Embryologically, CPK is initially present in the BB-form in all tis-

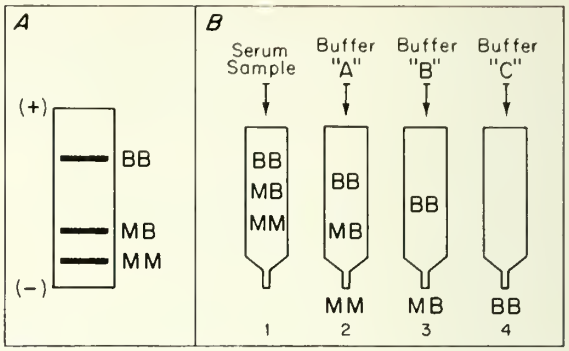

Figure 1.—Fractionation Methods. Showing fractionation of serum CPK into isoenzyme components by **A**, electrophoresis and **B**, DEAE-Sephadex column chromatography.

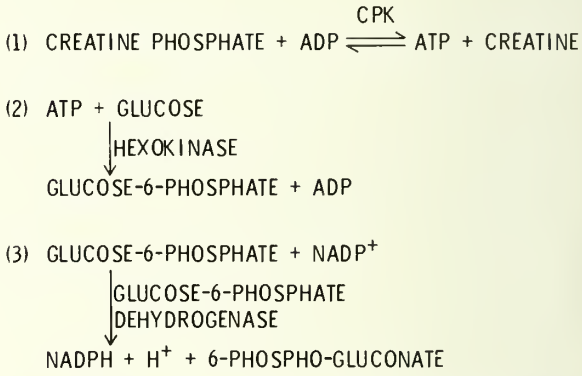

Figure 2.—Assay Method. Showing coupling of reverse CPK reaction **1**, with hexokinase **2**, and glucose-6-phosphate dehydrogenase **3**, mediated reactions to yield NADPH as product assayed.

sues.[12,33,35] In developing skeletal muscle, MB and then MM gradually appear in association with the development of myofibril contractile elements.[33,35,36] In the adult skeletal muscle, MM has been reported by some workers to be the only CPK isoenzyme present,[37-46,52] but numerous other workers report up to 4 percent of total CPK activity to be present as CPK-MB.[33,35,47-49] In brain, on the other hand, CPK-BB remains the predominant isoenzyme throughout embryological development and into adult life.[33,35] For myocardium, the embryological isoenzyme development is similar to that of skeletal muscle, except that in an adult approximately 20 to 30 percent of the total CPK activity has been reported to be CPK-MB.[31,33,35,41-43] An exception to this is the predominance of the BB-isoenzyme in the myocardium of chickens and some other avian species.[50,51]

As mentioned above, conflicting reports have appeared as to whether CPK-MB is present in human skeletal muscle. Other tissues reported to

contain CPK-MB include tongue, diaphragm and aorta—all of which contain CPK-MM as the predominant isoenzyme.[31,49] Also prostate, uterus, pancreas, intestine, bladder and stomach are reported to contain CPK-MB, but predominantly CPK-BB.[31,53] Lung, kidney, thyroid and adrenal have been reported to contain CPK-BB, but with either CPK-MM or CPK-BB predominating.[31,43,49,52,53] Liver has been found to contain low levels of CPK-BB.[49,52-54] In sharp contrast to the above results, Sobel and collaborators[38] and Galen and Gambino[43] surveyed a variety of human tissues obtained at surgery and were able to identify CPK-MB only in myocardium. Such conflicting results may derive from differences in extraction, fractionation and assay conditions as employed in the various laboratories. Therefore, although CPK-MB appears to be present in tissues other than myocardium, further research will be required to resolve this issue.

CPK-MB has been found to be both very specific and very sensitive for an acute MI. Usually, some four to six hours are required following the onset of the chest pain before CPK-MB becomes elevated in the serum of patients suffering an acute MI.[21,43,45,55,59] The peak of CPK-MB activity is usually observed within 12 to 24 hours, and then returns to normal levels within 24 to 48 hours, some 24 hours or so before total CPK activity returns to baseline levels. An incidence of up to 6 percent false positives[56] and up to 6 percent false negatives[57] have been reported for CPK-MB in the diagnosis of acute MI. Depending upon the methods employed, normal values for CPK-MB range from 0 to 3 percent of the total serum CPK activity. Compared to CPK-MB, LDH-isoenzymes have a reported incidence of 5 percent false-negatives and 14 percent false-positives in the course of an acute MI.[56] Reliance upon total LDH, CPK or SGOT results in even higher numbers of false positives[43,59-62]—further indication of nonspecificity in the diagnosis of an acute MI.

Although CPK-MB is of great value in a coronary care unit (CCU) setting, it is of lesser utility following cardiac surgical procedures. For procedures involving coronary bypass grafting, valve replacement or repair of congenital defects, CPK-MB is usually elevated postoperatively. The release of CPK-MB occurs intraoperatively, and by 18 hours after operation the CPK-MB has been reported back to normal levels in 74 percent of cases.[63,64] Neither the level of CPK-MB activity, nor the total CPK activity reliably indicates the occurrence of an acute MI in the perioperative period for cardiac surgical procedures.[63,65] Similar conclusions have been reported previously for LDH, SGOT and total CPK[66,67] although a recent study found a good correlation for LDH isoenzymes,[68] despite the fact that hemolysis can produce the same LDH isoenzyme profile in the absence of an acute MI. The highest levels of CPK-MB tend to occur with aortic valve replacement.[65] The contributing effects of hypothermia, fibrillation, defibrillation and post-pump sequelae following cardiac operations can only be speculated upon at present.[69] Establishing the diagnosis of an acute MI after a cardiac operation involves documenting appropriate ECG changes, but the appearance of Q-waves postoperatively may merely reflect an old MI and not the occurrence of an acute MI.[70,71] Myocardial scans have been reported to correlate with the occurrence of an acute MI, but again both false positives and false negatives are known to occur.[69,72-74]

CPK-MB release has also been reported to occur in a variety of circumstances in the absence of an acute MI, including the following: tachyarrhythmias,[22,75] atrial fibrillation,[22,75-77] cardioversion,[22,78] cardiopulmonary resuscitation,[78] cardiac catheterization,[43] multiple trauma,[43] dermatomyositis,[47] polymyositis,[35,41,47] viral myositis,[47] muscular dystrophy,[35,43,79] myoglobinuria,[43] coronary insufficiency,[61,76] angina pectoris,[61,76] congestive heart failure,[61,76] pulmonary embolism,[61,76] malignant hyperthermia,[43,80] hypothyroidism[44,81] and carbon monoxide poisoning.[80] Such documentation contrasts with numerous other reports of failure to detect elevated serum CPK-MB activity: despite a total CPK activity of 80,000 units per liter in acute rhabdomyolysis;[82] following a variety of thoracic, abdominal, genitourinary or orthopedic surgical procedures;[38,39] cardioversion;[83] cardiac catheterization;[38,55] pulmonary embolism;[83] convulsions;[77] angina pectoris;[83] trauma,[42] or hypothyroidism.[77,84] Sax and co-workers have reported on a series of 14 patients having elevated CPK-MB of 6 to 62 percent of the total CPK activity, despite normal or mildly elevated levels of total serum CPK activity.[11]

Although the concentration of CPK-BB is often reported along with CPK-MB, until recently CPK-BB has rarely been detected in serum. Efforts to prevent irreversible inactivation of CPK-BB activity have resulted in recent reports of elevated CPK-BB activity in patients with chronic renal failure,[85] gastric cancer[86] and malignant hyperthermia.[87]

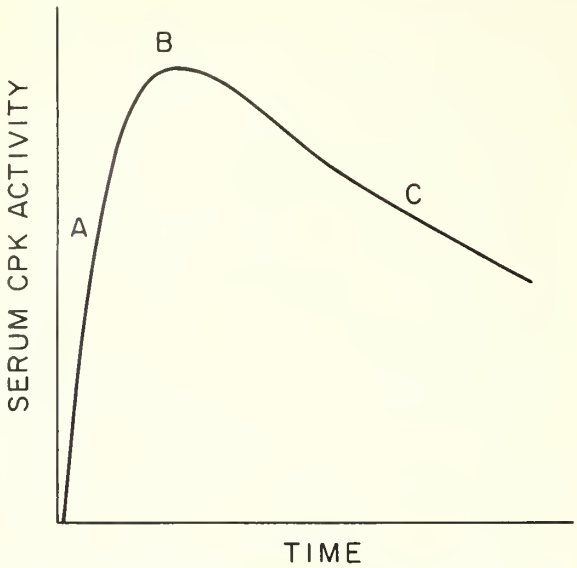

Figure 3.—CPK Kinetics. Showing release phase into **A**, serum; **B**, peak measured activity, and **C**, disappearance of CPK from serum. The slope of the disappearance segment has been used to calculate infarct size.

Itano has also reported increased serum CPK-BB in a series of 16 patients with conditions involving chronic lymphocytic leukemia, congestive heart failure and obstructive lung disease, fatal enterocolitis, syncope and cardiopulmonary resuscitation.[88] Conflicting reports have appeared relating elevated CPK-BB activity in serum with acute brain injury and central nervous system surgical procedures.[89-92]

Conclusions relating the degree and duration of serum CPK-MB elevation to the extent of myocardial infarction have been based on experimental protocols in animals.[54,93-96] Following the onset of an acute MI, the kinetics of both CPK release into serum from the area of infarction and subsequent CPK disappearance from serum can be shown by a plot of serial determinations of serum CPK activity as a function of time (see Figure 3). Estimates of infarct size in CPK-gram equivalents can then be derived from computer-assisted calculations based on the fractional disappearance rate of CPK from serum.[94] In such calculations, CPK-MB is assumed to be present only in myocardium. Furthermore, the size of the infarct, the rate of CPK-MB release, the rate of local CPK-MB inactivation and catabolism, and the disappearance rate of CPK-MB from serum, have all been assumed to be constant measures. The possible effect of variations in myocardial perfusion or reperfusion has been assumed to be negligible. Extracellular volume changes have likewise been considered insignificant. Although only 30 percent of the total CPK activity expected to be released from an area of infarction could be accounted for by the total amount of CPK activity detected in the serum of the experimental animals, the figure of 30 percent has also been considered a constant, and even applied to human studies.[97,98] In more recent work this figure is reported to be 15 percent[96,99] The reticuloendothelial system has been shown responsible for the disappearance of CPK activity from serum, with neither renal nor hepatic disease appreciably affecting the rate of CPK clearance.[6] Unresolved factors regarding CPK-MB and the extent of an acute MI include the reversibility of ischemic changes, including enzyme release,[100,101] the lack of precision in morphological estimates of infarct size,[93] the observation of diminished CPK activity in normal-appearing myocardial tissue bordering an infarction[94,101] and the role of reversible inhibition of CPK activity in areas of ischemia.[102] Therefore, except after cardiac surgical procedures, the degree and duration of CPK-MB elevation in serum can be used to approximate the extent of an acute MI, but a variety of factors may affect the reliability of such an index.[102,104]

The utilization of CPK-MB values in the diagnostic decision process requires a comparison with so-called normal values.[105] Significant differences in reported normal values for CPK-MB have been obtained from different analytical methods. Moreover, such normal values have usually been derived from populations of either healthy laboratory technicians or medical students, or from populations of hospital patients without cardiovascular disease. Perhaps a more appropriate reference population would include patients of similar age, sex, activity, medication usage and co-morbid diseases, but without evidence of an acute MI.

Despite the conflicting reports encountered during the survey of the current CPK-MB literature, the following conclusions have been reached: (1) CPK-MB appears to be present in tissues other than myocardium, including skeletal muscle, (2) CPK-MB appears to be released into serum under conditions other than myocardial infarction and (3) the degree and duration of CPK-MB elevation in serum is only an approximation, and not a reliable indicator of the extent of myocardial infarction.

CPK-MB appears to be the most sensitive and the most specific indicator of an acute MI availa-

ble, but astute clinical judgment is still required to reach the most reliable diagnostic decision and thereby to provide the most appropriate basis for subsequent management. Since CPK-MB may be released in conditions involving reversible myocardial injury, such as ischemia, congestive failure or tachyarrhythmias, other diagnostic criteria besides CPK-MB elevation alone would appear warranted to establish the diagnosis of an acute MI reliably. Unless serum analysis for CPK-MB is carried out within 12 to 24 hours after the onset of chest pain, false-negative results may ensue. The greatest predictive value of CPK-MB for an acute MI will be in the CCU setting, where the prevalence of acute MI is the highest.[106] The diagnosis of acute MI following cardiac surgical procedures will continue to be difficult because in most patients there appear to be elevated CPK-MB levels in the early postoperative period as a result of surgical trauma to myocardial tissue. Although myocardial scans may eventually contribute reliable, independent information relative to the diagnosis of an acute MI, further refinements will be required for this relatively expensive procedure before routine clinical use can be justified as reasonably cost-effective.

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Human Chorionic Gonadotropin (HCG) in the Treatment of Obesity

A Critical Assessment of the Simeons Method

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Injections of human chorionic gonadotropin (HCG) have been claimed to aid in weight reduction by reducing hunger, and affecting mood as well as aiding in localized (spot) reduction. We have tested these claims in a double-blind randomized trial using injections of HCG or placebo. Weight loss was identical between the two groups, and there was no evidence for differential effects on hunger, mood or localized body measurements. Placebo injections, therefore, appear to be as effective as HCG in the treatment of obesity.

THE TREATMENT OF OBESITY with diet and injections of human chorionic gonadotropin (HCG) was suggested by Simeons in 1954[1] but its effectiveness has never been clearly established.[2-5] In spite of the tenuous scientific basis for treating obesity in this fashion, the method has flourished in commercial weight clinics throughout the United States but with concentrations in certain locales such as Southern California.[6] Many of the commercial weight clinics advertise, operate on a high profit margin and offer physicians large sums of money to affiliate with them while making minimal demands upon physician time. Consequently, with strong financial motivations for the continued use of the Simeons method, critical objective evaluation seemed indicated. Among the values claimed for this treatment are less hunger; differential weight loss predominantly from the hips and legs, and less emotional difficulties such as depression during treatment. To put these allegations to the test the following randomized double-blind study was carried out.

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Patients and Methods

Patients answering an advertisement for participation in a treatment program for obesity were enrolled after payment of a deposit which was refundable upon completion of the study. The participants in this study were white women between 20 and 40 years of age, 152 and 172 cm in height, and 20 percent to 60 percent overweight.[7] They were all in good health and had not received HCG previously nor were they receiving any medication for obesity. Following physical and laboratory examinations, patients were randomly assigned into two groups, one receiving human chorionic gonadotropin and the other receiving placebo injections of diluent.

The drugs were prepared and dispensed by a local pharmacist, according to code number. Injections were given six days a week for six weeks and weights were obtained weekly. The measurement of hunger was evaluated by the method of Silverstone[8] and involves asking patients to mark a line between 1 and 9 based on their rating of hunger (1 = not hungry; 9 = maximum hunger). This measure was obtained at the beginning and at the end of treatment. The circumference of the midthigh, the chest, the hips at the iliac crest, and the mid-upper arm were measured at

the beginning and end of treatment to assess the possibility of localized fat reduction. Changes in mood during treatment were assessed using the Multiple Affect Adjective Check List, which rates anxiety, hostility and depression.[9] Instructions regarding diet, cosmetics and handling of patients at return visits were identical to those described in the study reported previously by Asher and Harper.[10] Upon completion of the course of injections the code was broken, and the data were tabulated and analyzed by analysis of variance using an IBM 370 computer.

Results

Twenty patients were enrolled in each group. The only significant difference between the two groups on the initial measurements was on the anxiety scale, where the HCG group were more anxious ($p < .05$) (Table 1). During treatment, seven patients in the placebo group and two in the HCG group failed to meet the minimum criteria for completion and were excluded from subsequent analysis (X^2 for difference in dropouts between groups using the Yates correction was 2.294; $p > 0.10$). The rate of weight loss is shown in Figure 1. There were no significant differences between the two groups at any time. The initial and final values for the anthropometric and psychological variables are shown in Table 2. There were no significant differences in the changes in any of these variables between the beginning and end of the treatment when comparing the patients who started and finished.

TABLE 1.—*Initial Values for Clinical Measurements in Two Groups of Patients*

	*HCG**	*Placebo**	*P†*
Body weight (kg)	81.4± 9.7	79.4± 8.4	.483
Circumferences (cm)			
Biceps	33.3± 2.8	33.0± 2.5	.881
Chest	91.2± 8.4	94.0± 7.1	.255
Iliac crest	104.6± 9.9	101.8±11.2	.402
Midthigh	58.2± 5.4	57.4± 4.2	.681
Hunger score	3.3± 1.1	2.8± 1.2	.203
Anxiety score	83.6±20.8	63.2±28.0	.017
Hostility score	69.1±22.0	71.6±28.3	.770
Depression score	74.1±24.5	69.4±23.3	.557

*N=20
†Probability determined by analysis of variance for group differences.

Comment and Discussion

In this trial of HCG and its diluent as a placebo, there were no significant differences in the two groups other than the greater anxiety in the HCG

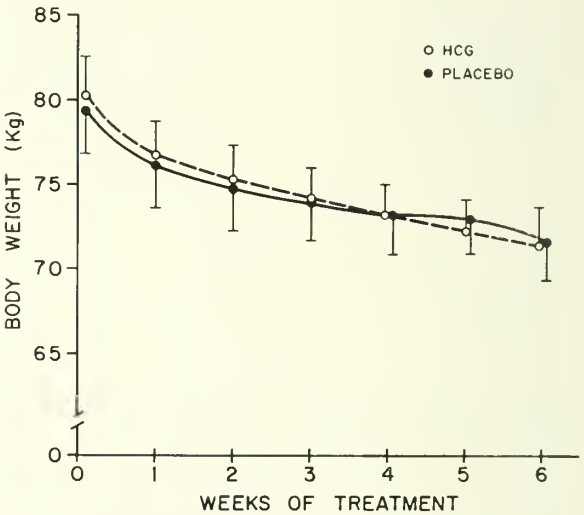

Figure 1.—Body weight during treatment with human chorionic gonadotropin (o) or placebo (•). There was no significant difference at any time.

TABLE 2.—*Initial and Final Values for Clinical Data in HCG-Treated and Placebo-Treated Patients*

	HCG		*Placebo*		
	Initial	*Final*	*Initial*	*Final*	*P**
Body weight (kg)	80.4±2.3	71.6±2.1	79.7±2.6	71.6±2.3	.366
Circumferences (cm)					
Arm	33.0±0.5	29.5±0.5	33.3±0.8	30.0±0.5	.733
Chest	91.7±1.8	88.6±1.5	94.0±2.0	89.4±1.8	.405
Iliac crest	103.9±2.3	95.0±2.0	100.6±3.8	92.5±2.3	.772
Midthigh	57.2±1.0	53.1±1.0	57.4±1.3	53.6±0.8	.285
Hunger score	3.3±0.3	4.4±0.5	2.9±0.3	4.2±0.5	.709
Anxiety score	85.1±5.0	64.5±5.4	67.1±8.1	65.4±6.1	.139
Hostility score	66.9±5.2	66.4±3.9	72.6±7.6	60.9±6.7	.318
Depression score	72.1±5.9	67.9±4.7	67.7±6.9	62.4±5.0	.913

*Probability determined by analysis of variance from F ratio for individual differences between initial and final values.

group before treatment. It is clear that patients lost weight quite satisfactorily indicating a high degree of adherence to the 500 kilocalorie diet. The injections of HCG, however, provided no additional effects that could not be accounted for by the diet alone. We conclude, therefore, that HCG used in the manner prescribed by Simeons does not enhance the rate of weight loss, nor does it significantly reduce hunger or change the ratings of anxiety, hostility or depression.

Although a number of other studies using HCG in the treatment of obesity have been carried out,[11] there appear to be only two that found HCG may be effective in treating obesity. The recent study by Stein and co-workers[4] was designed in much the same manner as the present study, except that mood ratings were not examined. However, they reached the same conclusion. With the now overwhelming body of evidence suggesting that HCG is no more effective than placebo in the treatment of obesity, it would seem that further efforts to perpetuate the Simeons method could only be financially motivated. Therefore, we feel that the 20 year history of the use of HCG in the treatment of obesity should come to an end because injections of placebo appear to be equally effective in all respects.[12]

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Protocol of Taking Blood Pressures in Children

Most often it's very difficult in an office practice to take blood pressures in patients under 2 and 3 years of age. However, I think there's a great need for us to be doing this; and we need to develop our techniques and our sensitivities to be able to determine blood pressures on every physical examination that we do on a child. I believe that pediatricians should devise a special protocol in taking blood pressures. . . . They should take a blood pressure with the patient standing or sitting; and then they should take the blood pressure following exercise. I think this would be terribly important. Many of us know that when a child first comes into a physician's office and is rather nervous, the child's blood pressure might be elevated as a result and perhaps the results of a blood pressure determination done at home by a parent might be much more significant, so that you can use this as a guideline.

—PHILIP L. CALGANO, MD, *Washington, DC*
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Acute Myocardial Infarction

Clinical Application of Technetium 99m Stannous Pyrophosphate Infarct Scintigraphy

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Acute myocardial infarction is being recognized as a spectrum of clinical subsets. This appreciation has been brought about to a large degree by the development of several new tools that can be applied clinically to aid in evaluation of patients with acute infarction, and in some cases to provide short- and long-term prognostic information. In the realm of noninvasive methods, several tests utilizing radiopharmaceuticals and scintillation cameras have emerged and are rapidly becoming reliable diagnostic parameters in patients with coronary disease and infarction. Technetium 99m (stannous) pyrophosphate (TcPYP) scintigraphy, one of the first of these techniques to find clinical use, has been shown to be an accurate indicator of acute transmural myocardial infarction and provides added sensitivity and specificity to the diagnosis. Increased diagnostic accuracy, the dimension of visible localization and the potential for infarct sizing promise physicians better understanding of a patient's clinical presentation and a more rational approach to management.

THE DIAGNOSIS of acute myocardial infarction can be made frequently from the characteristic clinical presentation. However, additional criteria have improved upon the accuracy of this diagnosis in both the classical as well as the more subtle or complicated cases. The development of new measures for use in diagnosis and treatment of infarction have been facilitated by modern theoretical and technological advances. The development of a reliable electrocardiogram and diagnostic criteria for its clinical use[1-3] was the first of these important advances. Later in the century the recognition and utilization of muscle enzyme elevations in the serum of infarction patients[4,5] allowed improved diagnostic sensitivity and specificity. The subsequent introduction of the myocardial specific (MB) fraction of creatine phosphokinase (CPK)[6-7] provided an additional increment of specificity to infarct diagnosis. However, the extreme sensitivity of the enzymatic method,[8] the temporal pattern of enzyme release[9] and the biological factors governing serum enzyme levels[10] present limitations even to this sophisticated diagnostic method. Paralleling these developments was the recognition of the prognostic implications of infarct localization and sizing.[11] However, neither electrocardiographic methods nor serum

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Dr. Shames is a recipient of a Research Career Development Award GM 70304 from the National Institute of General Medical Sciences.

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ABBREVIATIONS USED IN TEXT

CPK = creatine phosphokinase
MB = myocardial specific CPK
^{99m}TC = technetium 99m
TcPYP = technetium 99m (stannous) pyrophosphate

enzyme analysis have been able to reliably provide this important dimension of acute myocardial infarction.

While detection of experimental myocardial infarction using radiopharmaceuticals had been suggested in the early 1960's,[12] much of the current interest in clinical myocardial infarction scintigraphy was stimulated in 1973 by Bonte and co-workers.[13] These investigators showed in dogs that technetium 99m stannous pyrophosphate (TcPYP), already in common use as a bone imaging agent,[14] would localize in acutely infarcted myocardium. The use of skeletal imaging agents for infarct labeling was, in turn, partly based upon earlier work by D'Agostino[15] and Shen,[16] who described calcium accumulation in myocardial cells that had undergone necrosis. Since this early work in dogs, a good deal of laboratory and clinical experience with TcPYP infarct scintigraphy has been accumulated. Infarct scintigraphy has been shown to be diagnostic when conventional methods are unreliable or unavailable. Scintigraphy provides infarct visibility and may be the method of choice for noninvasive infarct localization and sizing in the clinical setting. However, controversy still exists regarding the full spectrum of its experimental and clinical utility and, therefore, its full impact on the management of patients with acute myocardial infarction. In the following text we review what is known of the biologic basis for TcPYP infarct imaging, the method for carrying out infarct scintigraphy and the range of its clinical application, and promising areas of clinical research now being investigated.

Infarct Labeling Imaging Agents

Most of the radiopharmaceuticals found to localize in acutely infarcted myocardium that have been investigated for clinical applications have been compounds of technetium 99m (^{99m}Tc). Although gallium 67 citrate has been shown also to localize in acutely infarcted myocardium,[17] it requires a one- to two-day interval between injection and imaging to allow adequate soft tissue clearance for infarct delineation, while its relatively high energy of emission and poor energy spectrum burdens the patient with a high radiation dose.

The use of ^{99m}Tc as a tracer in medicine was originally suggested because of its optimal physical properties.[18] Later introduced into clinical medicine as an imaging agent by Harper and co-workers,[19] this agent has subsequently been widely used for clinical scintigraphy. This popularity stems primarily from the abundance of its 140 KeV gamma photon emission, highly favorable for imaging by commercially available scintillation cameras; relatively short six-hour half-life, facilitating decreased radiation exposure; and favorable decay scheme, with an excellent parent-daughter relationship[6] allowing production from molybdenum 99 generators permitting ready supply of the radiopharmaceutical.[20] While several chelates of technetium have been developed to image infarction, pyrophosphate appears to be the most useful of these infarct localizing radionuclides. Technetium 99m tetracycline was popularized by Holman and colleagues[21] and was shown to provide a qualitative estimation of acute myocardial infarction size. However, areas of acute infarction can only be identified by focal myocardial deposition of the radionuclide at least 24 hours following its intravenous administration, making early assessment of infarction impossible and notably decreasing the radioactivity available for imaging. In addition, hepatic uptake of the radionuclide and a relatively low infarct-to-background radioactivity ratio diminish the accuracy and utility of this complex. Technetium 99m glucoheptinate localizes in acute infarction early, allowing optimal images to be obtained within hours after the event.[22] However, hepatic labeling, relatively low infarct-to-background radioactivity ratios and inability to image the infarct late following the acute event are characteristics that may limit widespread acceptance of this technetium chelate. A variety of other phosphate compounds have similarly failed to show clinical advantage over pyrophosphate.[23-25]

Mechanisms of Myocardial TcPYP Accumulation

Relationship to Cellular Events

Intramyocardial TcPYP accumulation in pathological amounts has been shown in several studies to be confined to regions of irreversible myocardial damage.[26,27] Extensive histopathologic ex-

aminations, mostly in acutely infarcted dogs, shows calcium and hydroxyapatite-like spicules in association with mitochondria, but also in other subcellular loci.[26,28] Originally thought to parallel this calcium accumulation, TcPYP uptake was found not to be reduced in necrotic hearts cultured in calcium-free medium.[29] Although phagocytosis of the radiopharmaceutical by leukocytes migrating into the infarct was also suspected of playing a role in tracer accumulation, recent evidence has shown this also to be unlikely.[26]

Relationship to Blood Flow

Although at higher levels of blood flow, TcPYP uptake seems to parallel the density of myocardial necrosis, Zaret and co-workers[28] and others[30] showed a low TcPYP uptake regardless of the extent of cell damage below a critical level of blood flow at approximately 30 to 40 percent of normal. Based in part on such experimental findings, it seems that the uptake of TcPYP into acutely infarcted myocardium, resulting in most cases from transient or permanent coronary occlusion, is related to residual and collateral blood flow to the area. Scintigraphic support for this hypothesis is provided by the so-called "doughnut" pattern of TcPYP uptake observed in dogs with proximal occlusion of the left anterior descending coronary artery where the central area of maximal necrosis and minimal blood flow is seen to have the least amount of tracer. Conversely, the peripheral zone with greater residual or collateral flow as identified by less intense necrosis shows maximal TcPYP uptake on the scintigram. This pattern has also been reported in humans with large anterior infarcts.[27,31]

Clinical Correlation

These cellular processes and blood flow alterations do not result in positive *in vivo* images until at least 12 hours after acute coronary occlusion, although radioactivity greater than normal is present in infarct tissue samples as early as four to six hours after infarction. In most patients with infarction, cardiac radioactivity is maximum at 48 to 72 hours, becomes less intense by 6 to 7 days and is usually absent by 10 to 14 days after the event. This is probably due to the progressive replacement of necrotic myocardium by granulation tissue and scar with progressive reduction in calcium deposits in the area of damage.[27] Patterns of uptake, however, are somewhat variable with some patients maintaining low levels of increased activity for several weeks and in some cases months. Persistently positive scintigrams have been reported[32] and will be discussed in a later section.

Scintigraphic Methods

Technetium 99m (stannous) pyrophosphate for infarct imaging is made available by a variety of methods from inexpensive prepackaged kits, and is the same material generally used for routine skeletal scintigraphy. In our laboratory, TcPYP is prepared according to a modification of the method of Huberty and co-workers.[33] The material has a 100 to 1 ratio of pyrophosphate to stannous ions, is quite stable and in previous studies has shown less than 3 percent free ionic pertechnetate. TcPYP scintigrams are best done using 37-phototube, high resolution scintillation cameras which are commercially available as both stationary and portable units. Studies in our laboratory are done with a Searle (Searle Radiographics, Des Plaines, Illinois) Pho Gamma IV stationary or Ohio Nuclear (Ohio Nuclear, Solon, Ohio) portable camera. A dose of 15 mCi of technetium 99m tagged to 5 mg of stannous pyrophosphate is most commonly used. Following an intravenous injection, approximately 50 percent of the dose is excreted by the kidneys and 50 percent is taken up in hydroxyapatite-bearing structures, mainly bone. Imaging is best carried

TABLE 1.—*Criteria for Interpretation of Technetium 99m Stannous Pyrophosphate Myocardial Scintigrams*

Intensity Grade

- 0 No accumulation of radionuclide in region of myocardium
- 1+ Slight, indefinite, accumulation of radionuclide in the cardiac region
- 2+ Definite accumulation of radionuclide in the region of the myocardium with activity less than that of ribs
- 3+ Definite accumulation of radionuclide in the region of the myocardium with activity equal to that of ribs
- 4+ Definite accumulation of radionuclide in the region of the myocardium with activity greater than that of ribs

Distribution

- DIFFUSE—Generalized radionuclide accumulation in the cardiac region apparently involving all aspects of the heart—without evidence of the ventricular cavity
- DISCRETE—Radionuclide accumulation in a specific region of myocardium

Final Interpretation

- NEGATIVE—Intensity grade 0 to 1+
- POSITIVE—Intensity grade 2 to 4+

out at least two hours after intravenous radionuclide administration, allowing adequate time for blood clearance. All images are obtained in the anterior, 45 degree left anterior oblique and left lateral projections at the 140 KeV technetium 99m photo peak, employing a 20 percent window and taken to 300,000 counts. Due to the temporal factors involved in TcPYP uptake, optimal time for imaging is two to three days after the clinically suspected event.

Criteria have been established for infarct image interpretation[34] (Table 1). Image radioactivity is called *discrete* if it is confined to a localized cardiac region and *diffuse* if generally apparent in all regions. Diffuse image abnormalities show no photopenic evidence of the left ventricular cavity and show radioactivity from the cardiac apex to the sternum. Images are graded according to the radioactivity in the cardiac region on a scale of 0 to 4+, where 0 represents no increase in radioactivity beyond background; 1+ represents a slight, faint or indefinite increase in cardiac radioactivity beyond background; 2+ represents a definite increase in cardiac radioactivity beyond background, but less intense than bone; 3+ represents increased cardiac radioactivity beyond background and equal to bone, and 4+ represents increased radioactivity in the cardiac region more intense than bone. Images graded 0 or 1+ are called normal, while 2+ to 4+ images are called positive. Figures 1 through 3 are examples of TcPYP scintigrams illustrating negative, discretely positive and diffusely positive images.

Computer Applications

Although some groups have developed computer programs for rib subtraction and image enhancement,[35,36] the need for image clarification is usually satisfied by obtaining multiple projections. Parkey and co-workers[37] estimate that image processing from this study may be helpful in only 10 to 15 percent of cases. Computer image enhancement can be useful when attempting quantitative scintigraphic analysis and infarct sizing as described below, but is otherwise most useful for display purposes. Routine infarct scintigraphy with TcPYP can be done and interpreted without computer assistance.

Sensitivity and Specificity in Acute Myocardial Infarction

The most important factor surrounding the potential routine clinical use of technetium 99m

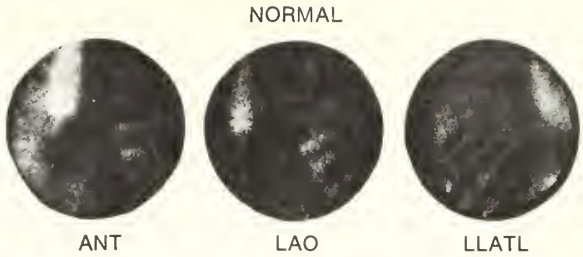

Figure 1.—Normal TcPYP scintigram. Shown are the normal scintigrams in a patient with chest pain but without acute infarction. (From Prasquier R, et al: Circulation 55:61-66, 1977.[51] With permission of the authors and the American Heart Association.)

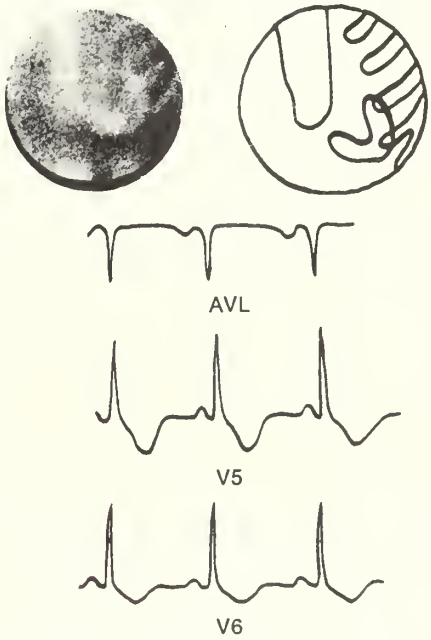

Figure 2.—Discrete positive scintigram. Above are the TcPYP scintigrams and three leads of the electrocardiogram from a patient with acute apical and anterior transmural myocardial infarction. The scintigram shows localized accumulation of radionuclide in these areas as illustrated in the schematic diagram at right. (From Botvinick EH, Shames DM: IEEE Transactions in Nuclear Science NS-23:1264-1267, June, 1976.[86] With permission of the authors and the IEEE.)

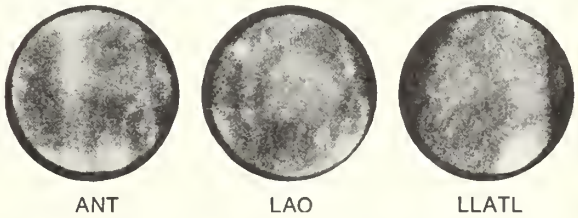

Figure 3.—Diffuse uptake. The TcPYP scintigram showing diffuse accumulation of the radionuclide in a patient with an acute subendocardial infarction. (From Prasquier R, et al: Circulation 55:61-66, 1977.[51] With permission of the authors and the American Heart Association.)

pyrophosphate scintigraphy is the diagnostic accuracy of the test. Initial experimental work in animals documented the sensitivity of infarct scintigraphy to small amounts of tissue damage. TcPYP scintigraphy successfully identified infarction weighing more than 3 grams.[35,38] Subsequently, Parkey and co-workers[34] reported the first clinical study of patients in whom acute myocarial infarction was suspected and who were admitted to a coronary care unit. They showed essentially perfect correlation with the presence of acute transmural infarction in 23 patients imaged up to eight days after the acute event. The discrete uptake of the radionuclide was appropriately correlated with the localized electrocardiographic changes. In all eight patients without other evidence of infarction, scintigrams were negative. After this report the same group described an apparent high correlation of positive scintigrams with the more difficult diagnosis of acute subendocardial infarction.[39] Of interest was the fact that 11 of their 17 patients with subendocardial infarction had a 2+ diffuse pattern according to criteria that had been established earlier[34] (see Table 1).

In the ensuing two years, however, numerous other investigators have reported reduced accuracy of these scintigrams for acute infarction. Abnormal scintigrams outside the setting of acute infarction, so-called "false positive" scintigrams, have been reported in both unstable[40,41] and stable[42] angina pectoris, after cardiopulmonary bypass,[42] with left ventricular aneurysm,[43] with valvular calcification[44] and postcardioversion.[45,46] Positive scans have also been described as persisting months to years following acute infarction,[47-49] following left mastectomy[47-51] and in congestive heart failure.[49] A review of these data, however, showed that most "false positive" scintigrams were diffuse and frequently of 2+ intensity. In fact, considerable controversy has developed regarding the nature and significance of the diffuse pattern of cardiac uptake.

Diffuse Uptake

We[51] evaluated more than 600 camera bone scans and myocardial scintigrams for evidence of TcPYP cardiac uptake. Among patients with clinical coronary disease, 16 percent were found to have diffuse radionuclide uptake in the cardiac region. However, a similar number of patients, 13 percent, without evidence of coronary disease also had the diffuse pattern of cardiac uptake. The frequent visualization of femoral vasculature in bone scans of noncoronary patients with diffuse TcPYP uptake and the presence of diffuse TcPYP uptake in patients who had undergone left mastectomy and consequently had diminished left chest tissue attenuation, indicated the possibility of blood pool imaging. Although attempts to monitor radionuclide blood levels in patients with diffuse TcPYP uptake showed no significant difference when compared with normals,[47] more sensitive methods of radionuclide analysis will be required to accurately detect quantitatively small, but statistically significant, differences. Well-known factors that could potentially play a role in the production of the diffuse pattern of uptake include camera field nonuniformity, radiopharmaceutical instability, tagging inefficiency, blood clearance variations, timing postinjection and the number of days after infarction. On the other hand, since some patients with diffuse uptake have definite infarction, disregarding diffuse uptake because of its nonspecific nature could decrease test sensitivity. Berman and co-workers[36] have recently suggested an approach to resolving this problem. They redefined the 2+ diffuse pattern of radionuclide uptake as equivocal rather than positive for acute myocardial infarction. This resulted in a dramatic improvement in the specificity of their image interpretations. Using this scheme, they found only 3 percent false positive scintigrams in 235 patients in whom studies for possible acute infarction were carried out.

Discrete Uptake

Although there is difficulty in interpreting the diffuse pattern of uptake, there is general agreement that the discrete pattern of cardiac uptake is quite specific for the presence of acute myocardial infarction. Several lines of investigation have supported the validity of this finding. Discrete image abnormalities have been correlated with electrocardiographic abnormalities and have been shown pathologically to parallel the site of infarction.[41] Additionally, the scintigraphic area of TcPYP uptake in such cases has been shown to relate favorably with infarct area and weight in animals[27,35,38] and agrees closely with enzymatic and functional measures of infarct size in man.[52,53] Distinguishing between discrete and diffuse uptake appears to clarify most discrepancies between the apparent accuracy of infarct scintigraphy as documented in numerous studies, with the myriad of reports of false positive scintigrams

described earlier. This is illustrated by the information regarding the persistently positive TcPYP scintigram. Malin,[47] Lyons[49] and others[42,48] have reported diminished specificity of TcPYP for acute infarction due to a significant number of positive images weeks and months following the acute event. Disturbed by these findings, we[54] carried out studies in 55 patients, nine days to ten years after a documented transmural infarction. In 14 of these patients imaging was done at the time of acute infarction and again at a later date. In each of the 14 patients in whom acute imaging was done, discrete scintigraphic abnormalities were noted. Among the entire group of 55 patients, 11 scintigrams remained abnormal, 9 with a diffuse pattern and 2 with discrete TcPYP uptake. In both patients with discrete uptake and in several with the diffuse pattern on remote images, a left ventricular aneurysm was found on angiographic evaluation. Therefore, discrete uptake occurred rarely in this study of remote infarction and when present was always related to a wall motion abnormality. Conversely, diffuse uptake was neither sensitive to, nor specific for, acute infarction—a finding similar to our overall experience. Previous investigators also reported a large percentage of both left ventricular aneurysm and diffuse uptake in their cases of persistent scintigraphic positivity. Studies by Ahmad and co-workers[42,43] while corroborating the overall accuracy of the discrete pattern of uptake for acute transmural infarction, also found a large percentage of patients with left ventricular aneurysm to have discrete radionuclide accumulation and suggested this as a possible cause of remotely positive scintigrams. Others have reported the occurrence of abnormal scintigrams in patients with left ventricular wall motion abnormalities and unstable angina pectoris.[55,56] In most cases, these nonspecific scintigraphic abnormalities were diffuse. The exact significance of TcPYP accumulation in these abnormalities is not certain, but may represent radionuclide deposition in regions of focal calcification or in spotty areas of myocardial necrosis, either at the aneurysm perimeter or, more widely, through an ischemic zone as suggested initially by Willerson.[39] Figure 4 shows complete scintigraphic clearing in a patient five weeks after an acute inferior infarction. Figure 5 shows the continued presence of diffuse uptake in the scintigram done in a patient ten weeks after a documented anterior infarction. Fig-

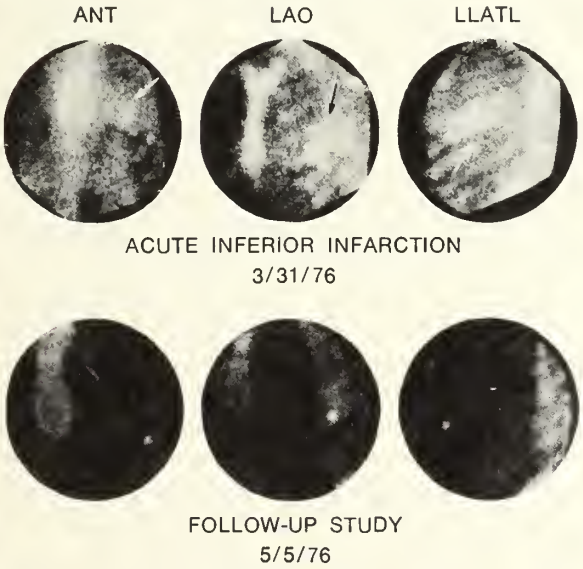

Figure 4.—Remote infarction. **Above (upper panel)** are the TcPYP scintigrams in the anterior (ANT), left anterior (LAO) and left lateral (LLATL) projections done at the time of acute inferior infarction. The scintigram is abnormal with a 3+ discrete inferior accumulation **(arrows).** In the **lower panel** are the scintigrams done in the same patient five weeks later. The patient was asymptomatic at the time of follow-up study and the image was normal with the exception of a persistent punctate rib abnormality.

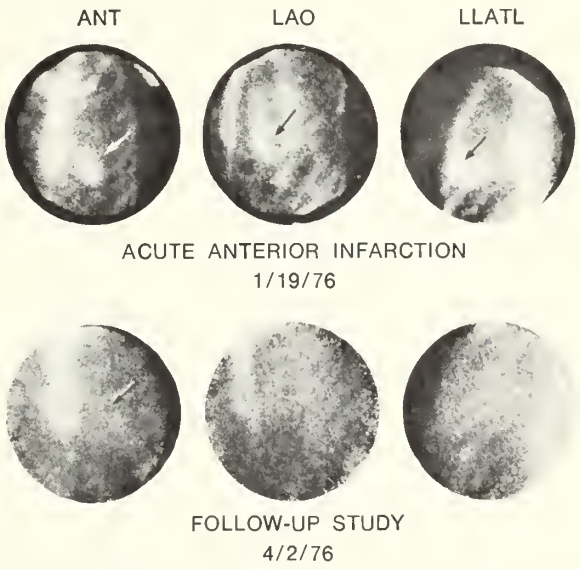

Figure 5.—Remnant diffuse uptake. **Above (upper panel)** are the TcPYP scintigrams in the anterior (ANT), left anterior oblique (LAO) and left lateral (LLATL) projections done at the time of acute anterior infarction. The scintigram is abnormal with a 4+ discrete anterior accumulation **(arrows).** In the lower panel are scintigrams done in the same patient three months later. The patient was asymptomatic at the time of repeat study, but a poorly localized 2+ diffuse pattern of radionuclide uptake was noted.

ure 6 shows the continued presence of a discrete scintigraphic abnormality 18 months after a documented anteroapical infarction. In both the patients concerned in Figures 5 and 6, left ventricular aneurysms were noted on angiography in the site of previous infarction.

Clinical Settings for Reduced Accuracy

"False positive" scintigrams related to discrete TcPYP uptake are not a common occurrence in the experience of most workers. Localized TcPYP uptake in the absence of acute infarction or associated left ventricular aneurysm has been reported with valvular calcification,[57] pericarditis,[58] tumor infiltration,[59] and penetrating and nonpenetrating trauma to the heart (J. T. Willerson, personal communication). Many of these conditions are related to myocardial necrosis, although not related to an acute coronary event.

Occasionally, scintigrams will be reported negative simply owing to the relation of the acute event to the time of imaging. Scintigrams reported negative, but done earlier than 24 hours after the event, should be repeated between two and three days after the event. Scintigrams which are negative, but done later than 1 week after the event, cannot exclude the diagnosis of acute infarction. On the other hand, an abnormal finding on an image done to document an acute infarction, but in the presence of a known remote infarction, must be clarified. The image abnormalities in the latter case can be related to the acute or remote infarction by correlating its location to the site and sequence of electrocardiographic abnormalities or by noting scintigraphic changes with serial images. Scintigraphic abnormalities associated with an acute infarction are more likely to be grade 3 and 4+, and will be found to be intense early and to fade when imaged serially, whereas abnormalities related to a remote event tend to persist unchanged. Such technical factors and other causes of "false positive" scintigrams must always be considered.

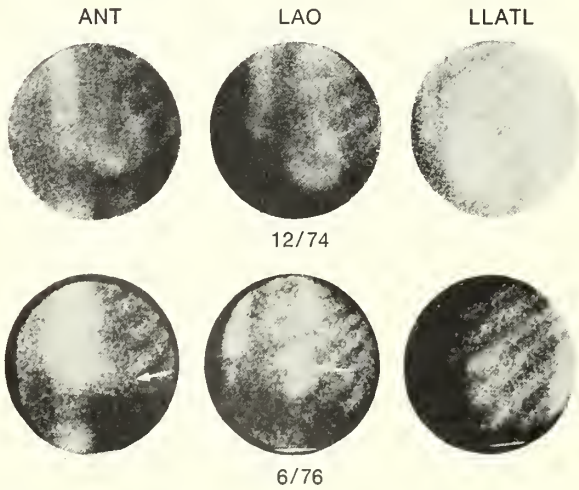

Figure 6.—Remnant discrete uptake. **Above (upper panel)** are the TcPYP scintigrams in the anterior (ANT), left anterior oblique (LAO) and left lateral (LLATL) projections done at the time of acute anteroapical infarction. The scintigram is abnormal with a discrete 3 to 4+ accumulation in the anterior wall and apex of the left ventricle. **Lower panel,** scintigrams done in the same patient 18 months later are shown. Although less intense than on the earlier study, the image remains abnormal with a similar 2 to 3+ accumulation **(arrows).** Measured acute infarct size was large and there was a documented anterior aneurysm.

Clinical Applications

Impact on Infarct Diagnosis: Transmural and Subendocardial Infarction

The availability of portable scintillation cameras and the simplicity of the technique make infarct scintigraphy feasible in community hospitals as well as major medical centers. Clinicians should demand, however, that the improvement in infarct diagnosis and evaluation be sufficient to justify the additional expense.

In an attempt to determine more quantitatively the relative clinical importance of TcPYP scintigraphy and its impact on the diagnosis of acute infarction, we reviewed[60] the records of 128 consecutive patients evaluated for possible transmural infarction or subendocardial infarction in our hospital from January 1975 to January 1976. The diagnosis of acute infarction was based on conventional electrocardiographic criteria, enzymatic criteria (CPK-MB of greater than 5 percent of total CPK) and scintigraphic criteria (discrete TcPYP myocardial uptake). Transmural infarction with new electrocardiographic Q waves was found in 35 patients, 32 with CPK-MB elevation and 34 with positive images. Subendocardial infarction was diagnosed in 28 patients, 27 with CPK-MB elevations. Seven of these 28 (25 percent) had positive TcPYP scintigrams. All of the 65 patients judged at discharge not to have infarction had negative scintigrams. It is important to note, however, that in 62 of these 65 patients there were new but nondiagnostic electrocardiographic changes or conduction abnormalities and in 30 patients there was elevated total CPK, usually related to a surgical procedure or intramuscular injection while in hospital. In 18 pa-

tients, 8 with transmural infarction, 2 with subendocardial infarction and 8 without infarction, there was elevated CPK-MB related to cardiac surgical procedures, cardiac catheterization, direct current countershock or myositis. Appropriately timed electrocardiograms or studies of cardiac enzymes had not been done in 12 patients, 2 with transmural infarction, 2 with subendocardial infarction and 8 without infarction, who arrived in the coronary care unit several days after the suspected event. Diffuse TcPYP uptake (2 to 4+) was found in 15 patients, 5 with subendocardial infarction and 10 without infarction. The data from this study were substantially confirmed by several subsequent studies on selected groups of infarct patients reviewed below and similar data for sensitivity and specificity were obtained recently by Berman and colleagues.[36] In an overall group of suspected infarct patients, therefore, TcPYP infarct scintigraphy seemed to be of greatest value in patients in whom there were nonspecific electrocardiographic or enzyme abnormalities (or both), or in patients seen a few days after the suspected event. In our study, a positive scintigram was in fact the earliest objective diagnostic indicator of infarction in some cases and as such was helpful in facilitating patient management and coronary care utilization.

Subendocardial Infarction

The subset of patients with possible subendocardial infarction is frequently a particularly troublesome diagnostic group. However, accurate detection could be of considerable prognostic importance. To determine the utility of TcPYP in this group, we evaluated the diagnostic accuracy of TcPYP in 29 patients with subendocardial infarction, 47 patients with transmural infarction and 41 patients with stable angina pectoris and no infarction. The same conventional criteria for diagnosis of infarction were used as in the previous study and scintigrams were done two to six days after the event. Our results are depicted in Table 2. Considering both the discrete and diffuse patterns of TcPYP uptake as positive for acute infarction, only 38 percent with subendocardial infarction were detected, compared with 90 percent with transmural infarction ($p<.001$). However, the discrete pattern was specific for infarction when compared with the group with only stable angina pectoris ($p<.01$). Other investigators have confirmed the somewhat decreased though variable sensitivity of the TcPYP scintigram for the diagnosis of subendocardial infarction. Sensitivities vary in these studies from 40 percent to as high as 90 percent,[39] a difference probably related to infarct mass and image interpretation.

TABLE 2.—*Comparative Diagnostic Accuracy of TcPYP Scintigraphy For Acute Myocardial Infarction*

	SEI	*TMI*	*SAP*
Number of patients	29	47	41
Negative	18	5	37
Diffuse uptake	6	3	4
Discrete uptake	5	39	0

SEI = subendocardial infarction
TMI = transmural infarction
SAP = stable angina pectoris (no infarction)

Evaluation Postcardioversion

Patients in whom cardioversion or defibrillation has been carried out, frequently because of unexpected hemodynamic collapse or in survivors of out-of-hospital sudden death, represent another group of patients in whom the presence or exclusion of acute infarction is of considerable importance for both acute and chronic management. Yet this group is frequently difficult to classify with certainty due to persistently abnormal cardiac enzymes and electrocardiograms related to the often traumatic resuscitative efforts or abnormal electrocardiograms due to previous infarction or conduction abnormalities. Although it was initially anticipated that the TcPYP scintigram might be of diagnostic use in this setting, several investigators reported findings, mostly in animals, suggesting that the TcPYP scintigram may be falsely positive due to the countershock alone.[45,46] In a recent study of 44 patients in whom direct current countershock was carried out at our institution, we did not find this to be the case.[61] The discrete positive TcPYP scintigram reliably distinguished between those patients who had suffered an acute infarction by other criteria from those who had not. Although electrically induced myocardial necrosis resulting in radionuclide uptake and also artificially induced chest wall uptake are legitimate concerns and may in fact occur when high dose repetitive discharges are delivered, in the clinical setting over a wide range of electrical energies and patient sizes, the discrete pattern of TcPYP uptake remained a discriminating and useful indicator of infarction.

Infarct Localization

The important dimension of visible localization

is provided by TcPYP scintigraphy in patients with acute infarction. Localization is relatively easy with 3 and 4+ discrete scintigrams, but is also possible with less intense uptake. In addition to the conventional three projections discussed in an earlier section, occasionally other degrees of obliquity will be added when heart location or rotation in the chest is unusual or TcPYP uptake in another projection cannot otherwise be localized. The sternum, spine and ribs are visualized and the location of myocardial uptake relative to these landmarks is noted. Hence, anterior wall infarction rotates with the sternum as the camera rotates more laterally. Conversely, posterior wall infarction, which can look similar to anterior infarction on the anterior projection, rotates away from the sternum. Inferior wall infarction visualizes as a plate-like extension of activity from the xiphisternum leftward as seen in the anterior projection. Figure 7 shows the utility of multiple projections in localizing acute anterior and inferior infarctions. Confirmation of appropriately rotating myocardial activity in multiple projections adds considerable security to the diagnosis. A great deal of care must be taken in interpretation of TcPYP activity that is less intense or seen in only one projection. Such noncardiac activity most frequently leads to misdiagnosis and additional views or computer enhancement may be of some aid. Subendocardial infarctions, when resulting in a positive scintigram, may be considerably more difficult to localize, but may be dramatic, as illustrated in Figures 8 and 9.

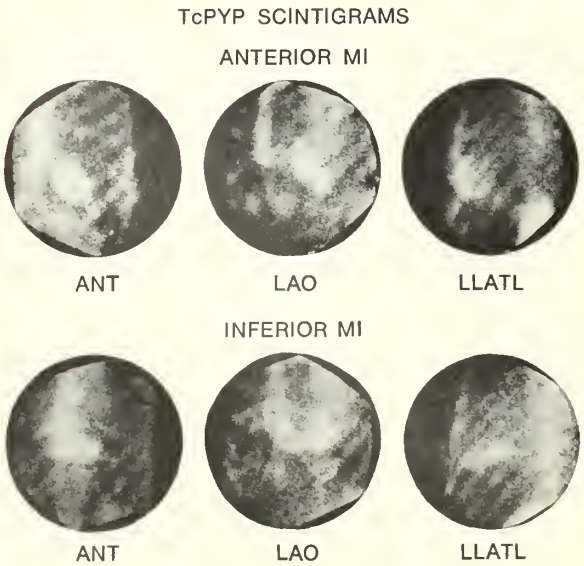

Figure 7.—Discrete uptake. Illustrated is discrete TcPYP uptake in patients with acute anterior **(upper panel)** and inferior **(lower panel)** transmural myocardial infarctions (MI). Note that radionuclide accumulation rotates with the sternum in the anterior infarction. The inferior infarction has a plate-like extension of radioactivity from the sternum leftward. In both cases, localization is enhanced with the use of multiple projections.

Infarct Extension

Recurrent chest pain or clinical deterioration (or both) following acute infarction can result from continuing necrosis and extension of infarction. This can at times be difficult to differentiate from other clinical entities including pulmonary embolism or the postmyocardial infarction syndrome.[62] Scintigraphy done shortly after the occurrence of symptoms can be diagnostic

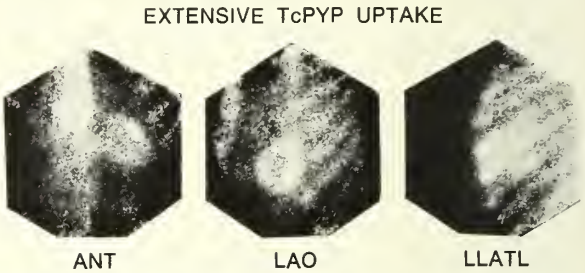

Figure 8.—Extensive TcPYP uptake. The scintigram above shows extensive intramyocardial radionuclide accumulation in a patient with massive acute subendocardial infarction. The presence of the photopenic left ventricular cavity confirms the myocardial localization and separates the study from those with diffuse uptake. In this patient total CPK was more than 1,000 units with 65 percent CPK-MB. However, the patient presented with only mild congestive heart failure which responded quickly to therapy.

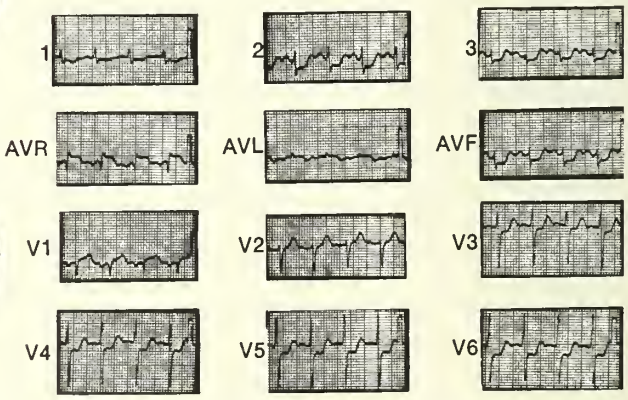

Figure 9. — Electrocardiographic correlation. Shown above is the electrocardiogram of the patient in Figure 8. Seen are widespread ischemic ST segment depressions which persisted. Diagnostic Q waves did not evolve. The maintenance of moderately good cardiac function in the presence of extensive necrosis may relate to the subendocardial distribution of damage.

for infarction as illustrated in Figure 10. The presence of an earlier scintigram documenting the infarct pattern of the original insult improves the diagnostic value of succeeding studies, both while the patient is still in hospital and during any subsequent events months or years later. Characterization of the infarction in this way and in association with other scintigraphic methods can help develop the full picture of the extent of irreversibly necrotic or reversibly ischemic myocardium (see below).

Right Ventricular Involvement

Acute infarction of the right ventricle, either exclusively or together with the left ventricular inferior wall, may be of considerable importance both diagnostically and therapeutically.[63] We[64] carried out studies in 26 patients with documented transmural infarction. Of 15 patients with inferior infarction by all criteria, including TcPYP scintigraphy, there was additional discrete uptake localized to the right ventricular free wall and often the inferior aspect of the interventricular septum in 5 patients. Gated blood pool scintigraphy, echocardiography and bedside hemodynamics by right heart catheterization using a triple lumen catheter, confirmed abnormal right ventricular size and function consistent with right ventricular infarction. The importance of these findings is considerable. Right ventricular infarction seems to occur more frequently than might be anticipated and when present is primarily responsible for the hemodynamic derangements seen and dictates specific therapeutic approaches which can be life saving. Patients with significant right ventricular infarction frequently present with low cardiac output and elevated systemic venous pressures due almost entirely to right ventricular pump failure. The clinical features can be confused with pericardial tamponade or more commonly cardiogenic shock due to left heart failure. In fact, the left ventricle in these cases can be relatively intact, but unable to maintain forward output due to volume starvation and may exhibit normal or low filling pressures. Standard diuretic therapy in this situation could exacerbate rather than improve the hemodynamic picture by further diminishing left ventricular filling and consequent cardiac output. Hence, right ventricular infarction can be masked in the initial clinical presentation and its quick noninvasive diagnosis by TcPYP scintigraphy represents an exciting advance in aiding management of these patients. Figure 11 compares the scintigraphic findings in two patients with inferior infarction, one with right ventricular involvement.

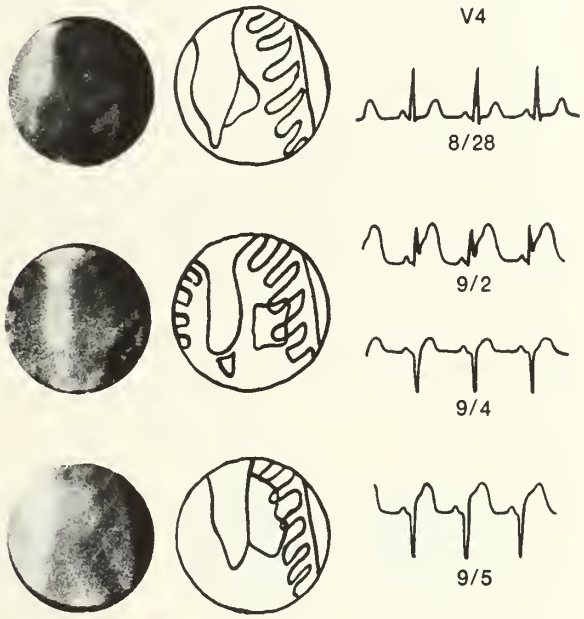

Figure 10.—Infarct extension. Shown are the TcPYP scintigrams from a patient initially admitted with chest pain and a normal electrocardiogram. The upper scintigram, done at admission, shows faint, diffuse uptake in the cardiac region. Intermittent chest pain continued and five days later the electrocardiogram showed acute injury and subsequent definite anterior and lateral infarction. The corresponding scintigram **(middle panel)** now shows a larger area of intense and discrete cardiac uptake. Chest pain resolved but subsequently returned with renewed ST segment elevation and ventricular ectopy. The scintigram done at that time **(lower panel)** documents a large discrete abnormality, considerably more extensive than previously and represented infarct extension. (From Shames DM, Botvinick EH: IEEE Transactions in Nuclear Science NS-23: 1237-1242, June, 1976.[85] With permission of the authors and the IEEE.)

Perioperative Infarction

The diagnosis of perioperative myocardial infarction, especially in patients in whom coronary artery bypass surgical procedures are being done, can be uncertain. Although in the absence of previous infarction, new electrocardiographic Q waves appear to be a specific finding for perioperative infarction,[65,66] many patients will in fact have antecedent infarction, conduction abnormalities or nonspecific repolarization changes on both preoperative and postoperative electrocardiograms. Similarly, findings in previous studies[14,66,67] have suggested that even the MB fraction of CPK may be present in the serum post-

operatively in the absence of clinically apparent infarction.

To evaluate the application of TcPYP infarct scintigraphy to the diagnosis of infarction following myocardial revascularization, we[68] obtained postoperative scintigrams, serial electrocardiograms and cardiac specific enzymes in 10 control and 51 revascularized patients. In all control patients electrocardiograms and scintigrams were negative for infarction, but in eight there were abnormal findings on studies of isoenzymes done after surgical operation. In eight revascularized patients there were diagnostic electrocardiograms, scintigrams and enzyme studies, but in two patients in whom postoperative scintigrams and enzyme studies were positive there were negative electrocardiograms. In 34 patients in whom postoperative electrocardiograms and scintigrams were negative, there were positive findings on isoenzyme studies, and in only 7 patients were all test results negative. Our data suggest that infarct scintigraphy is a useful adjunct to electrocardiograms for the diagnosis of perioperative infarction following revascularization. Similar conclusions were noted by Righetti and coworkers.[44,66] In both studies preoperative TcPYP scintigrams appeared helpful in gauging the presence of myocardial damage as well as for postoperative comparison. Figure 12 shows the positive infarct scintigram in a patient with an apical and lateral perioperative infarction. In this case enzymes were only mildly elevated and the electrocardiogram, although evolving new Q waves, became diagnostic only several days following scintigraphic infarct documentation and clinical deterioration.

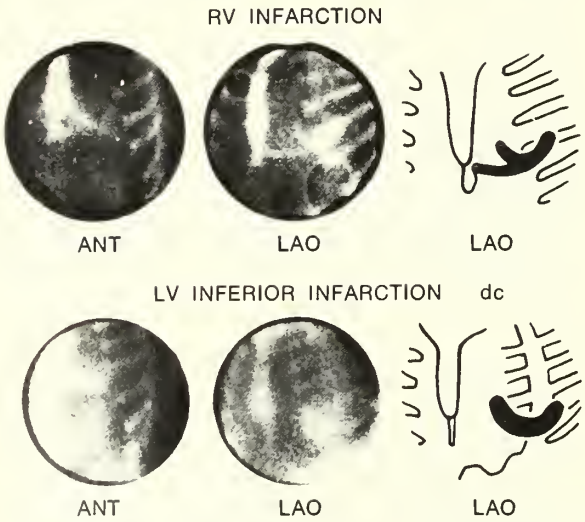

Figure 11.—Right ventricular infarction. Shown above **(upper panel)** are scintigrams from a patient with inferior wall infarction and right ventricular involvement. TcPYP labeling is seen to involve the distal intraventricular septum and right ventricle. The latter is anterior to the septum in the left anterior oblique (LAO) projection. The lower panel shows the TcPYP scintigram in a patient with typical acute inferior infarction. The LAO projection shows inferior accumulation to be considerably more posterior and separate from anterior bony structures.

Research Implications

Infarct Sizing

Death from acute myocardial infarction is a result of either arrhythmia or power failure in most cases. The advent of arrhythmia monitoring and coronary care units has reduced mortality from the former. Concomitant with this advance has been the development of intense interest in understanding the syndrome of power failure and its mechanisms. Several important reports have documented the relationship of infarct size to the development of power failure and, also, an inverse correlation between estimates of infarct size in man and subsequent survival.[11,69,70] This information has resulted in considerable activity concentrated on therapeutic interventions designed to limit the size of the infarction by salvaging ischemic but presumably not yet necrotic myocardium.[71,72] To objectively determine infarct prognosis and the effect of interventions, one must have a reliable repeatable non-

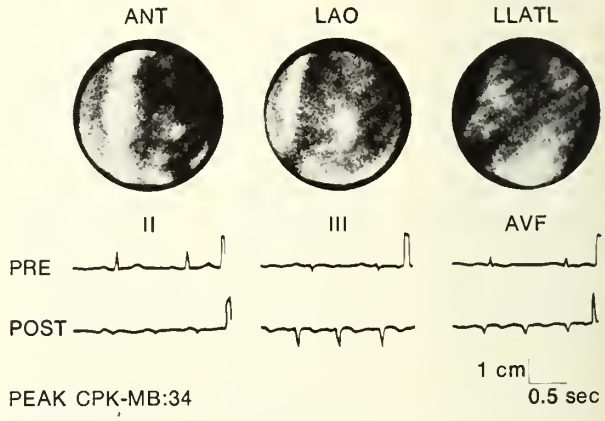

Figure 12.—Perioperative infarction. Shown are the postoperative scintigrams and representative preoperative and postoperative electrocardiograms of a patient in whom there was an inferoapical and lateral perioperative infarction. The peak CPK-MB obtained during the first two postoperative days was only 34 units. (From Klausner SC, et al: Circulation 56:173-180, 1977.[68] With permission of the authors and the American Heart Association.)

invasive method of measuring infarct size. To date, most commonly used methods for infarct sizing include precordial electrocardiographic ST segment mapping[73] and analysis of CPK serum enzyme curves.[74]

Since the recognition of TcPYP uptake in acutely infarcted myocardium, several groups of investigators have attempted noninvasively to judge the size of infarcts—both experimentally produced in dogs[35,38] and in humans.[21,52,53,75] In our animal work[38] the image infarct area and count rate 48 hours after infarction correlated well with pathologic infarct area and weight. This relationship was well maintained for anterior and lateral infarctions. Image area measurements obtained in a variety of projections in animals following experimental infarction showed the largest measured infarct area to correlate well with pathologic infarct area in cases of anterior infarction. Similar good correlations have been obtained using manual and computer assisted area measurements.[35] Recently we[53] evaluated scintigraphic infarct size in 26 patients with acute infarction. There was a significant negative correlation between image infarct area and left ventricular function as measured by stroke work index and ejection fraction. Other workers[52] have shown a relationship between infarct size as determined by CPK-MP and TcPYP image infarct area. Modifications of these methods may prove them complementary in acute infarct sizing. While noninvasive scintigraphic estimation of infarct size is an important goal,[76] it is still far removed from routine clinical application.

Other Scintigraphic Methods in Acute Myocardial Infarction

Technetium 99m pyrophosphate is a so-called "hot spot" imaging agent in that it selectively labels the area of interest—in this case, acutely infarcted myocardium. At present, it must be considered the scintigraphic technique of choice for this clinical purpose in spite of the limitations discussed. Potassium 43, rubidium 81 and more recently thallium 201 are intracellular cations which concentrate rapidly in viable, intact myocardial cells in relation to myocardial perfusion following intravenous administration and allow imaging in this initial distribution for approximately one hour after injection. Thallium 201[77-79] is the most commonly used agent due to its convenient 73-hour physical half-life and major 70 to 80 KeV emission. A significant coronary stenosis in one or more of the major coronary arteries producing a zone of relative ischemia at stress will result in decreased relative radioactivity in that area of myocardium when the radionuclide is administered during stress.[80] Similarly, at rest, scar will result in a "cold spot" due to decreased uptake of the radionuclide in the affected area. While this radionuclide is most commonly employed in association with stress testing to bring out an area of relative underperfusion due to coronary artery stenosis,[81,82] it is also used in some centers as an acute infarct imaging agent. Wackers[83] has recently demonstrated that thallium 201 scintigraphy is an extremely sensitive test for acute infarction early in the course, but gradually loses its sensitivity six hours or more after the event. However, a thallium 201 scintigram, when positive in the acute setting, cannot differentiate ischemia from infarction or fresh from remote infarction. Thallium 201 scintigraphy done with the patient at rest, weeks to months after the event, differs from TcPYP scintigraphy also in its inability to differentiate remote infarction. In the acute setting, thallium 201 presumably is identifying acutely ischemic myocardium in addition to the infarcted area, whereas TcPYP does not appear to produce positive scintigrams in ischemic but not infarcted myocardium.[26,27,57] Abnormalities on thallium 201 perfusion scintigrams are not specific for acute infarction, previous infarction or reversible ischemia, but must be correlated clinically. Correlation of abnormalities seen on a perfusion scintigram with those seen on a TcPYP scintigram may aid the identification of those patients who would be most benefited by aggressive therapeutic intervention. A patient presenting with power failure in the setting of his first myocardial infarction may present with a small TcPYP abnormality. Identification of a large concomitant perfusion defect would indicate that the functional decompensation was largely attributable to a large surrounding area of ischemic and perhaps salvageable myocardium and would be evidence in favor of aggressive treatment. Figure 13 shows infarct and perfusion scintigrams done on the same patient with acute inferior infarction.

In contrast to previously discussed methods, blood pool labeling with technetium 99m albumin or other complexes is primarily used as a noninvasive ventriculogram. This study allows a variety of measurements of ventricular size and motion.[84] With a computer, ventricular function

curves can be analyzed. Such noninvasive analysis of infarct patients will aid quantification of their functional disability and when done in association with other scintigraphic methods will identify the magnitude of loss related to reversible or irreversible conditions. Illustrating the combined use of these radionuclide procedures is a patient (Figures 8 and 9) in whom there was an extensive acute subendocardial infarction. This was documented by the development of the highest CPK-MB elevations seen in our institution during the past two years and serial electrocardiograms which showed sustained ST segment depression without the evolution of Q waves. The infarct area, as estimated from the extensive TcPYP seen on the scintigram, could well have been expected in a patient near death with cardiogenic shock. In fact, the patient was admitted with only mild congestive heart failure and improved rapidly using conventional therapy. A gated equilibrium radionuclide ventriculogram done soon after admission showed only mild, yet generalized, contraction abnormalities which correlated more closely with the patient's clinical presentation and course than the other scintigraphic measurements and helped us considerably in understanding the patient's clinical syndrome. Possibly, extensive myocardial damage in this case was related to relatively mild functional difficulty due to the subendocardial distribution of necrosis. Such cases further emphasize the heterogeneous spectrum of acute myocardial infarction. The correlation of information obtained from these scintigraphic procedures together with electrocardiographic and enzymatic data will lead to our greater understanding of the clinical subsets of this disease.

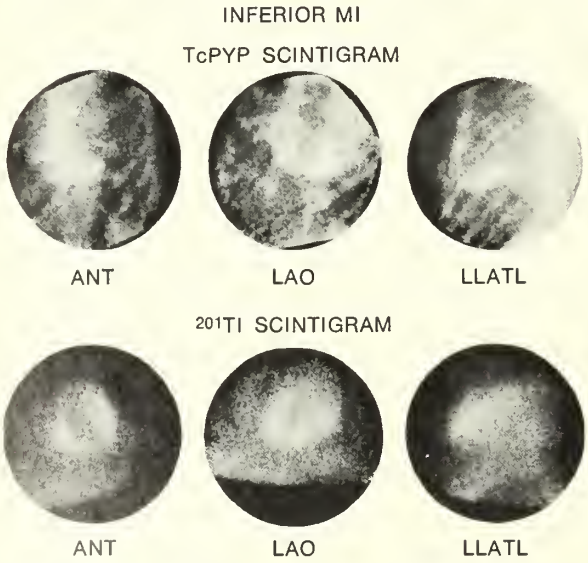

Figure 13.—Combined imaging. Shown in the **upper panel** are the TcPYP infarct scintigrams from a patient with acute transmural inferior infarction. There is a plate-like accumulation of radionuclide extending leftward from the sternum. The **lower panel** shows the Tl-201 scintigrams done at rest in the same patient. An area of relative hypoperfusion involving the inferior left ventricular wall is noted in all three projections and corresponds to the area of discrete TcPYP uptake in the infarct scintigram.

Conclusions

Technetium 99m infarct scintigraphy represents a new and exciting approach to the diagnosis and characterization of acute myocardial infarction. The discrete pattern of uptake is both sensitive and specific for acute infarction. TcPYP appears less sensitive to subendocardial infarction, but when seen in the discrete pattern is diagnostic. Discrete TcPYP abnormalities outside of the setting of acute infarction are infrequent, but may occur in patients with heavy valve calcification, calcified pericardium and left ventricular aneurysm. The diffuse patern of uptake is nonspecific. Clinical experience to date has shown TcPYP scintigraphy to be particularly helpful for infarct identification where the usual studies are nondiagnostic, unreliable or unavailable. The clinical value of scintigrams appears greatest in patients in whom there are electrocardiographic or enzymatic ambiguities—after cardioversion or cardiac surgical procedures, for example—and in patients with suspected infarct extension or involvement of the right ventricle. TcPYP scintigraphy has potential use in infarct sizing and therefore as a guide to acute infarct intervention. With other scintigraphic methods, TcPYP scintigraphy helps to differentiate reversibly from irreversibly damaged myocardium and in so doing aids physicians in understanding the full implications of the clinical syndrome of acute infarction, facilitating the institution of optimal therapy.[85-86]

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Handling a Hypoestronemic Teenager

With a teenager who might be hypoestronemic who comes in and says, "I want to have a good flow—I just don't like being different from the other girls. . . . What kinds of hormones do you use?" I've got a problem . . . . I wouldn't treat her, and she'd find another doctor. Because if I put her on a temperature chart and she was ovulating, there would be no reason for me to treat her and I would suggest that she might see someone else whose feelings were different. My counseling would be: (1) Let's find out if you're ovulating and (2) If you're ovulating, then Mother Nature has allowed you in a lucky fashion to have hypomenorrheic flows. When you want to get pregnant, look at how lucky you've been—your iron reserves are great.

—ALVIN F. GOLDFARB, MD, *Philadelphia*

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Specialty Conference

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Refer to: Collins DL, Marks L, Edwards D, et al: Management of infants with diaphragmatic hernia (Specialty Conference). West J Med 127:479-486, Dec 1977

Management of Infants With Diaphragmatic Hernia

WILLIAM L. NYHAN, MD, PH D:* *We shall launch into the case presentation by Dr. Marks.*

LLOYD MARKS, MD:† The patient was an infant boy weighing 3,440 grams (7.52 pounds). The primiparous mother had had an uncomplicated pregnancy. Labor and delivery were relatively easy, and the 1- and 5-minute Apgar scores were 7 and 7, with two points off for color and one off for respiration. Grunting, retracting and alar flaring were noted at birth and, rather than clearing with stimulation and suctioning, they seemed to get worse. There was a peculiar quality to the respirations. The baby seemed to be fighting hard to breathe but unable to get air into his lungs; it was a similar presentation to that of a child with upper airway obstruction; however, there was no stridor. The child was treated with 100 percent oxygen by bag, but he remained dusky and was rushed to the intensive care nursery.

On arrival, the patient's temperature was 36.7° C (98°F); pulse, 160; respirations, 70, and blood pressure, 70 by palpation. He was cyanotic, tachypneic and in pronounced respiratory distress. There was alar flaring. On examination of the chest, grunting, retractions and decreased breath sounds bilaterally were noted, with very little air movement. The heart was located in the right side of chest. The abdomen was soft and scaphoid. The findings in the chest and abdomen suggested a diagnosis of diaphragmatic hernia. This was confirmed by x-ray studies of the chest which showed abdominal viscera containing air in the left side of chest, as well as a significant mediastinal shift. An arterial blood gas assay showed a pH of 6.86, carbon dioxide retention of 80 mm of mercury, a base deficit of -22 and an oxygen pressure (Po_2) of 58 mm of mercury on 100 percent inspired oxygen. The patient was immediately intubated and ventilatory assistance begun. A nasogastric suction tube was inserted and repeated doses of salt poor albumin and bicarbonate were given with only slight correction of the acidosis to pH of 7.04. He was then given tromethamine (THAM) which raised the pH to 7.10 and the child was brought to the operating room. All of the abdominal contents except for the liver had entered the chest through a left diaphragmatic hernia which was identified and repaired by Dr. Collins. A left chest tube and gastrostomy were inserted. The procedure was tolerated well.

Postoperatively, a catheter was placed in the pulmonary artery so that we could monitor the pulmonary artery pressure and administer vasodilator drugs directly into the pulmonary circulation. Tolazoline was the first drug used, and pulmonary arterial hypertension was more or less

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successfully controlled. However, from time to time pulmonary artery pressure increased and even surpassed the systemic pressure, causing right to left shunting through the ductus. These episodes were associated with hypoxemia. After approximately 24 hours these episodes became more frequent. Thorazine and low doses of dopamine were both tried, but the patient's laboratory and clinical status continued to deteriorate.

At 48 hours of age the ductus arteriosus was ligated. Dopamine infusion was continued postoperatively and the mean pulmonary arterial pressure was maintained at 15 to 20 mm of mercury below systemic pressure. However, this situation was quite labile and affected the position, physical therapy to the chest and respirator settings. Administration of dopamine was tapered over eight days while pulmonary artery pressure was kept between 20 and 35 mm of mercury. We intentionally kept the patient alkalotic with pH over 7.5 and oxygenated to maintain Po_2 greater than 100 and less than 150 mm of mercury during this week of dopamine administration. After the administration of dopamine was stopped he was weaned to room air over two weeks. X-ray studies of the chest done each day showed a slowly expanding left lung. A large left anterolateral pneumothorax noted postoperatively progressively decreased in size and, when the chest tube was removed this area filled in with fluid, until it reached a state of equilibrium. A large amount of fluid, approximately 40 ml per kg of body weight each 24 hours drained from the chest tube for approximately two weeks and this tapered over the third week.

A second problem was transient renal failure. The infant was oliguric and azotemic for the first two postoperative days. Fluids were restricted and diuretics given and this was followed by a brisk diuresis.

A third concern was for the patient's neurologic status because of severe perinatal anoxia and acid base imbalance. The initial electroencephalogram showed a generalized nonspecific abnormality. The infant's condition could not adequately be evaluated clinically during the time he was paralyzed with pancuronium bromide (Pavulon®) and morphine. However, a recent follow-up electroencephalogram was considered normal for the patient's age, and findings on neurologic examination were normal at the most recent examination.

Figure 1.—Initial anteroposterior chest radiograph showing airways and mediastinal structures shifted to the right, with compression of pulmonary parenchyma. The left hemithorax was virtually airless except for a lucency whose configuration suggested a gas-filled viscus.

DR. NYHAN: *Thank you very much. Are there questions for Dr. Marks?*

QUESTION FROM THE AUDIENCE: How were the priscoline and dopamine given?

DR. MARKS: They were administered into the pulmonary artery catheter.

DR. NYHAN: *Let us turn now to Dr. Edwards, who will review the x-ray films of this patient.*

DAVID EDWARDS, MD:* Figure 1 shows the preoperative anteroposterior view of the chest. There was a virtually opaque left hemithorax with one gas-containing loop at the left base and a shift of the mediastinum to the right. There was very little if any aerated lung on the left. The abdomen was gasless in the portion seen.

Given these findings the differential diagnosis includes diaphragmatic hernia, eventration, and a variety of congenital intrathoracic masses. A large cystic adenomatoid malformation of the lung is usually included in the differential diagnosis when there are many gas-filled loops of small bowel in the thorax. In this instance not enough gas had entered the gastrointestinal tract for this to happen. In a postoperative film (Figure 2)

*Assistant Professor of Radiology and Pediatrics.

Figure 2.—Postoperative radiograph shows right pleural fluid with considerable lung expansion; the mediastinal structures were distorted, but almost midline in position. There was a left pneumothorax and chest tube.

the infant's mediastinum was seen to be rather bizarre in shape and this finding persisted. I think that this is related to the fact that the mediastinum was in the right hemithorax during development rather than in its normal position. A postoperative pneumothorax resolved slowly. The pulmonary vasculature on the right looked somewhat sparse. The left pulmonary arteries were very small, a finding consistent with a hypoplastic lung. I am sure there was some hypoplasia of the right lung as well, but not as pronounced.

DR. NYHAN: *Thank you very much, Dr. Edwards. It is a pleasure to turn now to Dr. David Collins who will discuss surgical treatment in this condition and review his experience with infants with congenital diaphragmatic hernia.*

DAVID L. COLLINS, MD:* The standard posterolateral diaphragmatic hernias vary quite a bit in the symptoms they produce according to how much compression of the lungs there is. Autopsy photographs of babies that never did breathe adequately have illustrated the problem faced by the baby in the case presented by Dr. Marks. In such patients the entire chest is full of abdominal viscera. Often the intestines are full of air, which certainly may interfere with survival. It is a common sequence of events for such infants to be resuscitated with a bag and mask, as in the case presented, when they do not breathe well in the delivery room. This can be harmful because the baby may just be able to get along with the degree of compression that it was born with and a little more air forced down into the stomach with the mask and bag will sometimes make a critical situation into an impossible one. This is difficult to avoid because, after all, other conditions that cause cyanosis and breathing difficulty in the delivery room are amenable to treatment with bag and mask. However, if one suspects a diaphragmatic hernia, one of the first things to be done is to put a nasogastric suction tube into the stomach to prevent any air getting into the gastrointestinal tract. Then, if ventilatory assistance is needed, an endotracheal tube should be used. Diaphragmatic hernia should be suspected if the chest is bulging, the abdomen flat and the heart sounds on the right.

It is possible to define a group of patients with diaphragmatic hernia in which there is a very high mortality rate. These are the babies that present with symptoms in the delivery room and require resuscitation at that time. If the arterial Po_2, while the baby is breathing 100 percent oxygen, is under 50 mm of mercury or, to put it another way, if the arterial-alveolar oxygen difference is greater than 560 mm of mercury preoperatively, or greater than 600 mm of mercury after repair of the diaphragmatic hernia, according to Raphaely and Downs[1] there is almost no hope for survival. We learned from the case presented here and from the case of another such patient seen recently that not only is the concentration of inspired oxygen important, but that the method of ventilation also is critical. In both of these cases when we changed from mechanical ventilator to hand ventilation, the arterial Po_2 improved from below 100 mm of mercury to over 200 mm of mercury. The most effective method of ventilation seems to be one in which there is a peak inspiratory pressure of about 35 or 40 mm of mercury and a rate of 40 per minute with a fairly short inspiratory time and no positive end-expiratory pressure (PEEP). If with vigorous hand ventilation and 100 percent oxygen, the baby's Po_2 cannot be raised to above 50 mm of mercury, survival with standard repair of the hernia is impossible. I brought this up at a recent meeting on the subject of diaphragmatic hernia at the American Academy of Pediatrics,

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and none of the 50 pediatric surgeons in the audience had ever had such a baby survive.

The surgical repair can be carried out through the chest or the abdomen. We more commonly use a subcostal incision. When we open the abdomen sometimes the stomach or often just the liver is visible, and everything else is in the chest. It is quite easy to deliver the organs down into the abdomen. The size of the hole in the diaphragm bears little relationship to the severity of the hernia. There can be a fairly small hole but nevertheless a very large hernia. The larger holes tend usually to be fairly severe hernias but there is not a strict correlation.

The usual explanation for the bad results in cases of severe diaphragmatic hernias is the presence of pulmonary hypoplasia. Such patients, of course, do have hypoplastic lungs—half to two thirds of normal weight. This has always been said to be the cause of death. It has never made much sense to me, because of one fairly simple observation that I have made repeatedly: most of the patients look very good indeed postoperatively and they continue to do so for a few hours. When the hernia is repaired the anesthesiologist immediately comments that the pulmonary compliance has improved and the baby looks pink. As soon as the patient gets back to the ward and the first blood gas results arrive, the Po_2 is wonderful, perhaps in the 200's. The patients continue in that fashion for 12 to 18 hours through what I call the honeymoon period. It usually lasts less than 24 hours. Then the patient begins to get anoxic, and usually after standard measures aimed at correcting the Po_2, the acidosis and the ventilation, no matter what we do, the babies in this severe group die. At autopsy, of course, the lungs are found to be hypoplastic. It never has been explained adequately to me, if lung hypoplasia is the explanation, why then can they temporarily oxygenate so well. I have felt that there has to be some pathophysiologic change that takes place that interferes with oxygen transfer some 12 to 18 hours postoperatively and that this might be amenable to treatment. Certainly, expanding the lungs is not the answer. During this period we use the chest tube to keep the pressure more or less atmospheric in the empty chest by letting air in, if necessary, so as not to overexpand the lungs and possibly cause a pneumothorax.

In 1972 we made an observation in the intensive care unit that one of our babies with a severe diaphragmatic hernia had fairly severe differential cyanosis, with cyanotic lower extremities and pink upper extremities and head. This had to mean there was right-to-left shunting through the ductus. We then measured three more infants and obtained this correlation: the two that had more shunting had died and the two that had less shunting lived. I subsequently learned that a paper had been published at about this time in which there was a similar implication—that babies with bad diaphragmatic hernias have pulmonary vascular obstruction or fetal circulation. This was published by Murdock, Burrington and Swyer[2] from the University of Toronto. Another paper[3] from the same institution described work with fetal lambs that showed that the creation of a hernia *in utero* with subsequent delivery yielded baby lambs with pulmonary vascular obstruction and pulmonary hypertension.

These observations suggested that perhaps this was something that we could do something about. The **first patient** in whom we tried was born at University Hospital. Dr. Searle Turner catheterized the baby and found that the pressures in the main pulmonary artery and the aorta were similar. Actually the main pulmonary artery pressure was somewhat higher. Cardiac catheterization showed there to be a large patent ductus. We obtained a cineangiogram which showed that nearly all of the right ventricular output went through the ductus and then into the aorta and there was almost no pulmonary blood flow at all. Dr. Turner then tried giving some vasodilator drugs. He gave 4 mg of tolazoline (Priscoline®) and nothing seemed to happen. Then he tried a dose of chlorpromazine and again nothing much seemed to happen. He went on and finished the examination by cardiac catherization and was about to send the baby back to the ward when he noted that the mean pulmonary artery pressure had fallen below the mean aortic pressure, and at the same time the Po_2 rose. The baby had come to the catheterization laboratory with an arterial descending aorta Po_2 of 34 mm of mercury and went back to the ward with a Po_2 of 220 mm of mercury. The baby looked good for another hour or two and continued to receive tolazoline by drip at about 5 mg per hour. The baby rapidly became resistant to tolazoline and died.

We felt that this was a rather significant experience because it represented the first time that anything had ever changed that downward trend one so often sees in the postoperative course of a patient with a diaphragmatic hernia. At about

that point I presented the work here at a Grand Rounds, and one of my thoughts was whether or not we might be able to ligate the ductus in these babies, and whether that would prevent the right-to-left shunting and encourage pulmonary blood flow. Ligation might also perhaps make it possible to administer rapidly acting vasodilators such as acetylcholine directly into the pumonary artery and achieve delivery to the lungs where we wanted it without getting short-circuited off into the systemic circulation. I had asked several cardiologists about this, and they all had the same answer: "No, you will never get away with it. With that degree of pulmonary vascular obstruction the ductus is acting as a vent. If you tie off the ductus, the patient will immediately go into right ventricular failure and die." Dr. William Friedman was in the audience when I discussed this, and he said he did not think that that would happen because the foramen ovale is open, and, if the baby has to shunt right to left, it will be able to do it through the foramen.

We had reviewed our autopsy material on diaphragmatic hernias and found that in every case there was a very large patent ductus. The ductus in these patients is also quite long because the pressure on the mediastinum stretches the ductus out and makes it into a most remarkable looking structure. The first time one sees it, it appears to be the aortic arch. Also in reviewing our autopsy material, we found, as Dr. Friedman had said, that the patients each did have a very large patent foramen ovale which would seem to offer an adequate means of egress for the right ventricle. We then went ahead, and with our next severe diaphragmatic hernia patient we managed it in this way.

Preoperatively the Po_2 was 50 mm of mercury on 100 percent oxygen indicating the patient was in the 100 percent mortality group. The Po_2 went up to 400 mm of mercury after operation. In this patient we ligated the ductus and repaired the hernia at the same time through the left side of the chest. We kept the forced inspiratory oxygen (FIO_2) at 100 percent for the first 20 hours postoperatively, and then felt encouraged enough to start lowering it and brought it down to more or less the physiologic range. The baby's arterial oxygen came down as we would expect. Thereafter it started to drop below 100 mm of mercury and we started increasing the FIO_2. By 50 hours the baby's Po_2 had again dropped even with an FIO_2 of 100 percent and at this point we were in trouble. Nevertheless, this was notably different from most cases of diaphragmatic hernia because in most of them difficulties begin well before 24 hours, usually within 12 to 18 hours. So ligation of the ductus appeared to change the baby's course for the better.

We then used different drugs, starting with tolazoline, then chlorpromazine, which worked for a few hours. When we gave tolazoline, there was a temporary increase in Po_2 and the same thing happened when we gave chlorpromazine, but neither one was effective for very long. However, when we used acetylcholine, there was a definite improvement in Po_2 which again was temporary. As long as we could keep the pulmonary artery pressure below the aortic pressure, the Po_2 was adequate in the descending aorta. However, ultimately the pulmonary artery pressure rose, the aortic pressure fell and the baby died. Again, although we felt that we had shown in this patient that we were doing something with these drugs and the ligation of the ductus, it was not enough to provide a good result in this baby. Actually, at autopsy a small bowel volvulus with gangrene was found. We asked the pathologist to look at the pulmonary arterioles and they were not permanently damaged, as they would be in pulmonary hypertension of the permanent sort. The layers were thickened in some of them but it was more spasm than permanent fibrosis, indicating that it might be a temporary phenomenon.

The next patient, **the second,** presented with severe cyanosis requiring resuscitation in the delivery room and endotracheal intubation. The Po_2 was 40 mm of mercury while 100 percent oxygen was being given preoperatively. This baby was operated on transabdominally, and the left diaphragmatic hernia was repaired without ligating the ductus at that time. The baby did very well and Po_2 values were in the 200's for about eight hours. Difficulties began at 20 hours of age, and we ligated the ductus. It was a huge patent ductus. After ligation of the ductus the Po_2 again went up to 250 mm of mercury for a few hours but it soon came down again to below 100 mm of mercury. At that point we began drug therapy. Administration of tolazoline did not seem to work in this baby at all, but therapy with chlorpromazine, given at a rate of 5 mg per hour, did lower the pulmonary artery pressure and increase arterial Po_2. We were able to lower the inspired oxygen value, keeping it in the 80 percent range for the first four days, and the Po_2 stayed in the

50 to 100 mm of mercury range for most of the postoperative course. When the Po_2 began dropping again we started administration of acetylcholine, and there was an immediate jump in the aortic Po_2. We were able to reduce the dose of acetylcholine from 200 μg per hour and keep the baby's Po_2 in a physiologic range. At about the time that we started the acetylcholine therapy, the pulmonary artery pressure began to drop below the aortic pressure. This is something that has been quite consistent in all of the five patients that we have managed in this way. As long as we can keep the pulmonary artery pressure lower than systemic, even a few millimeters lower, the babies can oxygenate. However, once pulmonary artery pressure exceeds systemic levels the babies become anoxemic. This patient is now almost two years old and doing quite well.

The case of our **third patient,** who did not survive, is illustrated in Figure 3. Again, there was a nice jump in Po_2 at the time that we repaired the diaphrgmatic hernia, but then the Po_2 dropped in spite of the administration of 100 percent oxygen. We tried some drugs preoperatively in this patient, chlorpromazine and tolazoline, but they did not seem to do much. We ligated the ductus and there was a pronounced jump in Po_2. Part of this, of course, is mechanical because we are measuring these Po_2 values in the descending aorta; I think one would expect a jump in Po_2 in the descending aorta when you ligate the ductus in a patient with a right to left shunt. At any rate, we fairly soon had to get on to treatment with acetylcholine in rather high doses, milligrams rather than micrograms, and it never really did much for this baby. We had to give huge doses in order to try to keep the pulmonary artery pressure below the aortic pressure, and if we did that and also gave 100 percent oxygen, we kept the Po_2 in the 50 to 100 mm of mercury range for at least some of the time, but it soon began to tail off in spite of huge doses of acetylcholine. At autopsy, multiple pulmonary emboli were found which must have come from the cardiac catheter in the pulmonary artery. From that point on we decided to use an end-hole catheter, an umbilical artery catheter.

In our **fourth patient** treatment was successful. It was managed like the previous two: repair of the hernia first, then repair of the ductus when

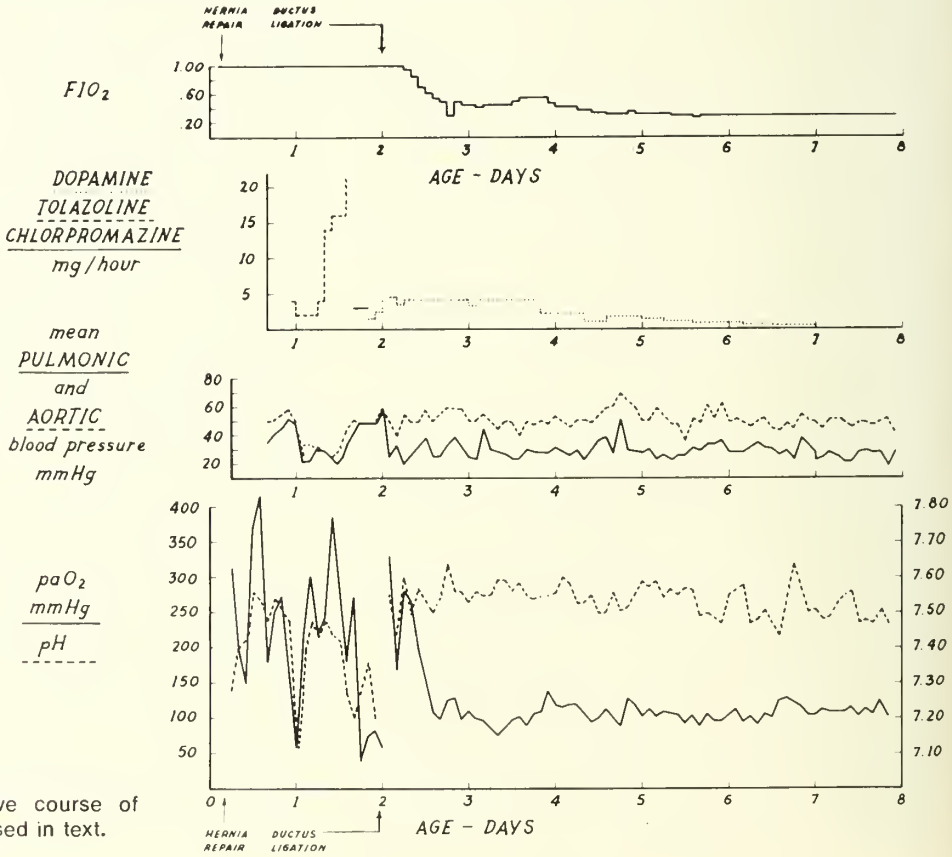

Figure 3.—Postoperative course of the third patient discussed in text.

the baby became anoxic. Acetylcholine in rather large doses was required for about two weeks. Finally the pulmonary circulation opened up, and the baby began to oxygenate, and we stopped the acetylcholine therapy. That baby is now at home, doing well.

Dr. Marks presented our most recent patient which brings the total experience to five. There were three survivors. I believe all five were in the 100 percent expected mortality group. This is a very exciting development for me, but I do not think that three cases really prove the point. What we need is more cases, and I now am in the process of trying to organize a nationwide registry. Many pediatric surgeons feel that they would like to use the drugs only, and it may well be that with more vigorous ventilation and perhaps using higher drug dosages we could get some of the babies through without ligating the ductus. I think, however, if one needs to use acetylcholine, which is neutralized in a few seconds in the blood stream, ductus ligation is essential. I hope that in a few years I can present a report and that the numbers will indicate that we are doing something significant.

DR. NYHAN: *Thank you very much, Dr. Collins. Your results are impressive. Our next speaker is Dr. Stanley Kirkpatrick.*

STANLEY E. KIRKPATRICK, MD:* There are a few brief comments I would like to make. The first is in reference to the cause of pulmonary hypertension in these patients. In babies with diaphragmatic hernia it is not yet clear whether there are fewer pulmonary arterioles or whether there are increased media in the resistance vessels of the lungs as seen in patients with persistent fetal circulation. However, it is apparent that the major difficulty in these patients is the hypoxia from poor pulmonary perfusion which results from a pronounced increase in pulmonary vascular resistance.

In treatment I agree with Dr. Collins that oxygenation of these infants should be quite vigorous, maintaining Po_2 at 100 to 150 mm of mercury. If the Po_2 falls the pulmonary vascular bed constricts and it is difficult to dilate it again. If mechanical ventilation is not adequate to maintain good pulmonary perfusion, pharmacologic intervention is indicated to dilate pulmonary arteries and increase cardiac output (dopamine, acetylcholine, tolazoline and prostaglandin E_1). Thorazine has been used empirically but its mechanism of action remains unknown.

We have reasoned that it would be worthwhile placing a catheter in the pulmonary artery in order to obtain the maximum dilating effect on the pulmonary vascular bed. With the large right-to-left ductal shunt shown at catheterization, we felt that ligation of the patent ductus acriosus would be helpful in potentiating pulmonary perfusion. Before ligation of the patent ductus arteriosus we placed the catheter preferentially in the patient's right lung, which appeared to be the least hypoplastic. Once the ductus was ligated we pulled the catheter back into the main pulmonary artery. I prefer to employ an end-hole only catheter which is flexible in order to diminish the possibility of intimal damage, clotting and emboli to the lungs which are inevitable complications when catheters are left in place for prolonged periods. I prefer to insert the catheter via the femoral approach rather than through the umbilicus since it is easier to manipulate the catheter into the right or left pulmonary artery from the leg than it is through the umbilicus. The normal route of blood flow from the umbilicus is directly across the foramen into the left atrium, and a catheter tends to take that same course. I therefore place the catheter percutaneously into the right femoral vein and advance it with the help of a wire guide into the pulmonary arteries.

QUESTION FROM THE AUDIENCE: Why do you not ligate the ductus at the same time you repair the diaphragmatic hernia?

DR. COLLINS: It is hard to predict at the time of the original surgical procedure just how bad a case it is going to be. In some of the patients the intestines may be filled with air; the patients may look very bad before the hernia repair but not really be in the severe group. They get by with just the hernia repair.

QUESTION FROM THE AUDIENCE: How much time would it add to do the ductus ligation?

DR. COLLINS: If you use a thoracic approach for the combined procedures, ligating the ductus would add perhaps another ten minutes to the operation. If you do it as a separate operation it does not really seem to be all that much of a problem for the baby. These infants are maintained paralyzed anyway. It is another trip to

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the operating room and a little anesthetic; the operation takes perhaps half an hour as a second stage. The babies tolerate it very well.

QUESTION: Do you think pancuronium bromide or morphine might directly affect oxygenation?

DR. COLLINS: That is a good point. I have noticed that as soon as the relaxant drugs start to wear off and the baby starts to struggle a little bit or try to breathe on his own, the Po_2 goes down.

In conclusion, I would like to acknowledge the help that we have received with this very critically ill baby from Dr. Ronald Coen, Associate Professor of Pediatrics and Co-director of the Special Care Nursery, the interns, the residents, the fellows, the nursing staff in the intensive care unit and also from Dr. Kirkpatrick, who put those catheters just where we needed them. This was an extremely ill baby, and it took a lot of team work to get him through.

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Medical Treatment of Meniere Disease

A DOUBLE BLIND STUDY was done on meclizine (Bonine®) in patients with Meniere disease at the University of Florida. Therapy with the drug was so dramatically effective when used in appropriate amounts that the patients would come back (and we didn't know which bottle was which) and they'd say, "You know, I had to go back to that bottle A, Doctor, because with the other one, I kept getting sick." So, meclizine is the drug of choice for me now.

As far as diazepam (Valium®) is concerned—I avoid using it in patients with Meniere disease. I've had to wean patients from Valium; they've been hooked because of indiscriminate use. If you take an average person, 15 mg of Valium a day over a long period of time is (if you can use the term) an "addicting" dose. And, if I have to use Valium in such patients, then I'll use 2 mg three times a day. . . . I don't think we should give a person a problem greater than the problem he came to us with.

—ROBERT KOHUT, MD, *Irvine, CA*

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Hodgkin Disease

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and Robert C. Siegel, Associate Professor of Medicine and Orthopaedic Surgery, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SHOHET:* *Significant advances have been made in the management of hematologic malignancies in the past ten years. We have asked Dr. Samuel R. Newcom to discuss Hodgkin disease this morning at Medical Grand Rounds.*

DR. NEWCOM:† Hodgkin disease is an uncommon disease representing about 1 percent of all cancers.[1] However, it has created significant interest and excitement in the medical community because of its complex management and its very responsive nature to chemotherapy and radiation therapy.

Although all ages are affected, the patient is usually a young adult, 20 to 40 years old. The patient most frequently presents with an asymptomatic enlarged lymph node. Most often the cervical lymph nodes are involved first, the left somewhat more frequently than the right. Axillary nodes are involved on initial presentation less often and inguinal presentation is quite rare. There is a propensity for mediastinal involvement particularly in the nodular sclerosing variety.[2]

Clinicopathologic Correlations

The histopathologic classification and clinicopathologic correlations of Hodgkin disease are shown in Table 1.

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†Samuel R. Newcom, MD, Assistant Clinical Professor, Associate Chief, Hematology and Oncology Clinics.

The most important physician in the initial evaluation is the hematopathologist utilizing the diagnostic criteria developed by Lukes and coworkers and modified at the Rye symposium in 1966.[3,4] This is a four-part classification scheme which has significant prognostic implications.[5,6]

Lymphocyte predominant Hodgkin disease is one of the rarer histologies representing 10 to 15 percent of the total in most series. Of these patients 80 to 90 percent have early-stage disease confined to one side of the diaphragm, stage I or II, and they rarely have symptoms. The five-year survival is very good (85 percent).

The largest group of patients are those with nodular sclerosing Hodgkin disease, usually representing 40 to 50 percent of the total, but at some institutions representing as much as 75 percent of the Hodgkin disease population. More than two thirds of these patients have stage I or II disease, only a third of the patients have symptoms and the five-year survival is quite good (70 percent).

The other large group of patients with Hodgkin disease are those with mixed cellularity. This group represents 30 to 40 percent in most series and tends to be an older group. Only half of these patients have stage I and II disease. Also, half have symptoms and the five-year survival is significantly worse than for patients whose tumors have the preceding two histologies (38 percent).

The rarest category is lymphocyte depletion. This histology represents 5 to 10 percent of the

ABBREVIATIONS USED IN TEXT

ABVD = doxorubicin hydrochloride (Adriamycin®), bleomycin, vinblastine sulfate (Velban®) and imidazole carboxamide
MOP = nitrogen mustard, vincristine (Oncovin®) and procarbazine
MOPP = nitrogen mustard, vincristine (Oncovin®), prednisone and procarbazine

total in most series. These patients are the oldest group and most (70 percent) have advanced disease and symptoms. The five-year survival is poor (35 percent).

Histopathology

Figure 1 shows specimens of tissue in Hodgkin disease.

In lymphocyte predominant tissue one sees occasional, classical Reed-Sternberg cells which are binucleate with inclusion-like eosinophilic nucleoli. The Reed-Sternberg cells are large, measuring 30 to 50 microns in diameter. Mononuclear Reed-Sternberg variants may also be seen but are not diagnostic. These cells appear in a sea of well-differentiated nonmalignant lymphocytes.

Nodular sclerosis is characterized by two findings: (1) thick bands of collagen fibers and (2) lacunar cells. During formalin fixation these rather atypical Reed-Sternberg cells undergo shrinkage of the cytoplasm leaving lacunae. The cellular infiltrate is variable and tends to be pleomorphic.

Mixed cellularity Hodgkin disease is generally seen with abundant Reed-Sternberg cells and a pleomorphic cellular infiltrate characterized by multiple eosinophils, as well as histiocytes, lymphocytes and plasma cells.

The rarest histology, that of lymphocyte depletion, is characterized by the presence of multiple bizarre, highly malignant Reed-Sternberg cells and mononuclear variants with little in the way of normal cellular reaction.

TABLE 1.—*Histopathologic Classification and Clinicopathologic Correlations of Hodgkin Disease*[5,6]

Classification (Lukes, et al[3,4]*)*	*Total Percent*	*Stage I or II Patients Percent*		*B Symptoms* Percent Patients*		*5-Year Survival Percent*
Lymph predominance	10-15	8/9	89	0/9	0	85
Nodular sclerosis	40-50	63/92	68	32/92	35	70
Mixed cellularity	30-40	37/65	55	30/65	43	38
Lymph depletion	5-10	3/10	30	7/10	70	35

*Fever, weight loss, night sweats.

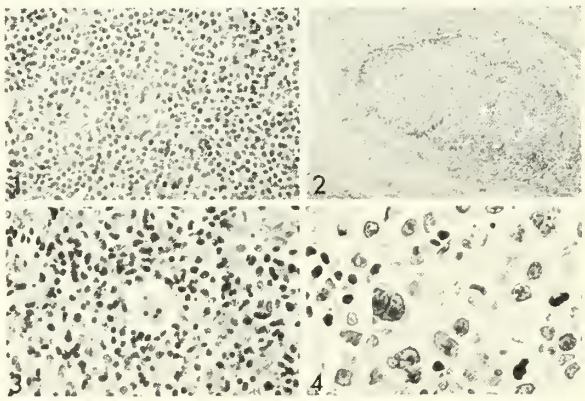

Figure 1.—Hodgkin disease tissue classified according to Lukes and co-workers,[3,4] showing: **1**, lymphocyte predominant, **2**, nodular sclerosis, **3**, mixed cellularity, **4**, lymphocyte depletion. (Courtesy of M.E. Kadin, MD, Dept. of Pathology and Lab. Med., University of Washington.)

Clinical Evaluation

The staging classification of Hodgkin disease is shown in Table 2.

Initial clinical evaluation should include a few specific studies that have been established as being useful. The history provides information regarding B symptoms. Three statements classify a patient as having B symptoms: (1) loss of 10 percent of the body weight in the preceding six months, (2) fever and (3) night sweats, particularly when volunteered in the history.

Physical examination will provide information

TABLE 2.—*Staging Classification of Hodgkin Disease*

Stage	*Definition*
I	Single lymph node region (I) or a single extralymphatic site (I_E)
II	Two or more lymph node regions on the same side of the diaphragm (II) or a localized site of extralymphatic involvement plus one or more node regions on the same side of the diaphragm (II_E)
III	Lymph node regions on both sides of the diaphragm (III) which may include the spleen (III_S) or a single extralymphatic site (III_E) or both (III_{SE})
IV	Diffuse or disseminated involvement of one or more extralymphatic organs: marrow = M+, lung = L+, liver = H+, pleura = P+, bone = O+, skin = D+

The classification is labeled A if the patient has none of the *three* B symptoms: (1) fever, (2) night sweats, or (3) unexplained loss of 10 percent or more of the body weight in the six months preceding admission.

about the clinical stage (for example, lymph nodes above or below the diaphragm, palpable spleen, liver).

Routine laboratory studies should always be made. Anemia, if seen, correlates well with B symptoms and is generally that of chronic inflammation;[7,8] it may occasionally be microcytic in spite of adequate iron stores. A rare patient will present with Coombs positive hemolytic anemia.[9] Thrombocytosis may be present and correlates with B symptoms and poor prognosis.[10] Liver function tests are very unreliable. The alkaline phosphatase tends to be the most sensitive indicator of liver involvement but is associated with many false positives.[11] The nonspecific acute phase reactants, as measured by the sedimentation rate and the serum copper value, are useful tests primarily for monitoring relapse but should be measured during the initial evaluation to be followed during remission induction. Because of the likelihood of mediastinal involvement, an x-ray study of the chest is mandatory and whole lung tomograms are quite useful, particularly if the diagnosis is nodular sclerosis or if there is hilar or mediastinal involvement. Bipedal lymphangiography is mandatory in the initial evaluation and useful for documenting para-aortic lymph node enlargement as high as L-2. With the Jamshidi bone marrow biopsy needle, one can now discover most of the 8 to 10 percent of patients who have bone marrow involvement provided bilateral iliac crest biopsy studies are done. Computerized axial tomography, ultrasonography and isotope scanning have not been helpful, in our hands, for routine initial evaluation.

Following these studies, a decision must be made regarding further evaluation of the abdomen. A multidisciplinary group representing medical oncology, hematology, hematopathology, radiation therapy, diagnostic radiology, peritoneoscopy and surgery is helpful at this juncture.

Peritoneoscopy

Peritoneoscopy (see Table 3) is a method that has been used at our institution for staging and restaging. A 2 cm incision is placed, utilizing local anesthesia, immediately below the umbilicus. The peritoneoscope is introduced into the abdomen after the peritoneal cavity has been filled with air. Tumor nodules on the liver can be visualized directly and, through a separate locally anesthetized area, a biopsy needle can be inserted and directed at the nodule (Figure 2). Randomly taken biopsy specimens of the normal appearing liver can also be obtained. Following the biopsies, hemorrhage can be visualized, tamponade can be applied from above and, if the bleeding does not stop, surgical procedures can be undertaken. In addition, some investigators roll the patient into the right decubitus position, the omentum falls away and the spleen can be visualized for evidence of tumor nodules. Splenic punctures have been carried out in more than 100 patients.[15] Using a probe, the undersurface of the liver can be visualized as well and other structures can be manipulated as necessary to obtain adequate visualization (Figure 3).

The advantage of peritoneoscopy over laparotomy is, of course, the decrease in morbidity and mortality; 2 to 4 percent of cases have morbidity, as compared with about a third in staging laparot-

Figure 2.—Hodgkin disease tumor nodule as visualized with the peritoneoscope. Biopsy needle is directed at the nodule percutaneously. (Courtesy of M. Lieberman, MD, Dept. of Medicine, University of California, San Francisco.)

TABLE 3.—*Peritoneoscopy in Hodgkin Disease*

Investigator	*Number of Patients*	*Morbidity*		*+Liver*	*+Bone Marrow*	*+Liver (at Surgery)*
		Peritoneoscopy	*Laparotomy*			*— Peritoneoscopy*
Coleman (1976)[16]	31	4%	39%	..	..	1
Beretta (1976)[15]	121	2.4%	31%	7	7	2
Bagley (1973)[17]	47	12%		13	..	..

omy.[15,16,17] No deaths have been reported. The sensitivity is quite good, although occasionally liver disease is missed by peritoneoscopy.

Indications for Staging Laprotomy

Indications for laparotomy following sequential evaluation including bone marrow biopsy studies, lymphangiogram and negative peritoneoscopy are shown in Table 4.

Beretta and co-workers[15] suggest that one can safely avoid laparotomy when the peritoneoscopy, lymphangiography, and bone marrow biopsy studies are negative, if there is disease involving only high cervical lymph nodes with very little chance of intra-abdominal involvement. In addition, laparotomy can be avoided if there is disease confined to the mediastinum which also has little chance of intra-abdominal involvement.[18] If the patient has B symptoms, and the institution consulted would deliver radiation therapy plus chemotherapy, then the risk of laparotomy is also not warranted; and certainly, if the patient is at high risk for surgical operation, laparotomy should be avoided.

Therefore, laparotomy becomes most useful in those patients that have low cervical nodes, particularly left supraclavicular nodes. If one plans to deliver just radiation therapy to more advanced stages and desires assurance that there is no liver involvement, laparotomy is indicated. If the lymphangiogram is equivocal, surgical operation is necessary to determine if there is involvement of retroperitoneal lymph nodes. If there is a large spleen, the radiation therapist usually asks that the spleen be removed, not only to document involvement, but to reduce the port-size and spare the left kidney and left lower lung field from radiation damage. If an oophoropexy is to be done, a complete staging laparotomy should be carried out as well.

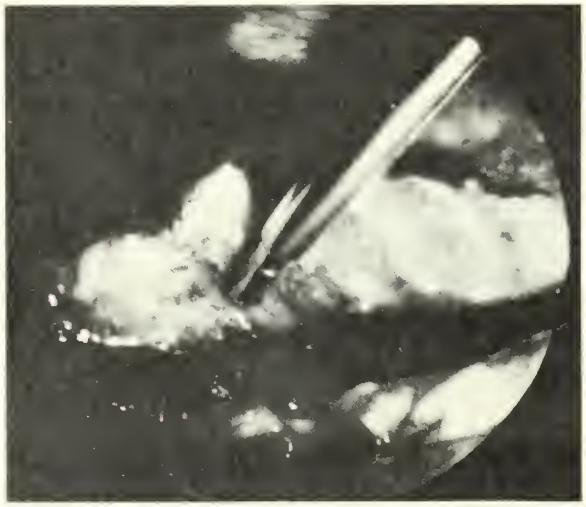

Figure 3.—Tumor nodule on the undersurface of the liver visualized through the peritoneoscope with the aid of a probe inserted percutaneously. (Courtesy of M. Lieberman, MD, Dept. of Medicine, University of California, San Francisco.)

Laparotomy

If a staging laparotomy (see Table 5) is indicated, the radiation therapist should accompany the patient to the operating room to assure that the following are carried out: (1) Abnormal lymph nodes noted on a lymphangiogram should be excised and the excision should be documented by a kidney, ureter and bladder study before closure of the abdomen. (2) Because 10 to 15 percent of patients with normal lymphangiograms will have positive para-aortic nodes, random

TABLE 5.—*Staging Laparotomy*

Excisional biopsy of abnormal nodes
Random excision of normal nodes
Splenectomy
Liver biopsies
Open marrow biopsy
Oophoropexy
Radioopaque clips

TABLE 4.—*Indications for Laparotomy Following Sequential Evaluation Including Bone Marrow Biopsies, Lymphangiogram and Negative Peritoneoscopy**

Laparotomy Most Useful If:	Laparotomy Unnecessary If:
1. IA with low C-nodes or IIA, IIIA if radiotherapy alone planned	1. IA with high C-nodes and −LAG
2. Suspicious LAG, and RT alone planned	2. IA or IIA with mediastinal disease only
3. Splenomegaly	3. IB, IIB, IIIB or IIIA if chemotherapy planned
4. Fertile women requesting oophoropexy	4. High-risk patients

*Adapted from Beretta et al.[15]

LAG = lymphangiogram
RT = radiation therapy

lymph node excisions must be carried out in at least three different locations when there are no abnormalities noted on lymphangiography. (3) Splenectomy should be done; an enlarged spleen is involved half of the time, a normal sized spleen a third of the time.[12] The pathologist should serially slice the spleen using a large knife and looking for the white tumor nodules of Hodgkin disease. (4) Similarly, the surgeon should examine the liver closely for the presence of the surface nodules of Hodgkin disease, as well as take a large wedge biopsy specimen from the right lobe and two or three needle biopsy specimens from each lobe. (5) If four Jamshidi bone marrow biopsy specimens have been obtained before laparotomy, the open marrow biopsy is considered optional; it is currently carried out through a separate incision over the right anterior iliac crest. (6) Oophoropexy in women who are menstruating is useful in salvaging ovarian function,[13] and (7) at the completion of the procedure, radiopaque clips should be applied to the splenic hilum, to any enlarged lymph node masses, and to the lateral borders of the ovaries so that the radiation therapist can identify these structures.

Oophoropexy

The ovaries lie in close proximity to the iliac lymph nodes and will be included in the inverted-Y radiation therapy field. Therefore, the patient will be sterilized if the ovaries are left in their usual location. To attempt to salvage ovarian function, the ovaries and fallopian tubes can be dissected free and the ovaries moved into the midline and sutured to the uterus with radiopaque material.

At Stanford University 97 women have undergone this procedure followed by total nodal radiation therapy.[14] Some of these women have also received MOPP (nitrogen mustard, vincristine [Oncovin®], prednisone and procarbazine) chemotherapy. In spite of using a 10 cm lead shield, the ovaries receive about 350 to 400 rads by scatter when the usual 4,000 to 4,400 rads is delivered to the inverted-Y field. Many of these women are amenorrheic for a short time, but about 60 percent of them recover normal menses following therapy. At this time there are seven women who have become pregnant, one with twins, one with two sequential births, and one who underwent therapeutic abortion. All of the term babies have been normal in appearance and there has been no evidence of acute leukemia. It is too early to estimate the risk of acute leukemia to the child or the risk of recessive chromosomal damage to the succeeding generations.

Radiotherapy

Johnson has had significant criticism of this aggressive approach to staging utilizing laparotomy and, for many years, has proposed that patients be treated without doing invasive abdominal studies.[19,20] He uses his own data to support that concept with respect to patients who are staged with lymphangiograms and bone marrows alone, and have clinical stage IA, IIA, IB, or IIB disease. Johnson has shown excellent survival treating such patients with total nodal radiation therapy yielding six-year survival rates of 98 percent for asymptomatic patients and 76 percent for patients with B symptoms.[19]

On the other hand, Glatstein, who first proposed doing staging laparotomies,[21] has shown that if all sites of disease are documented, patients can be treated with a smaller radiation therapy field, and the survival rates will be identical to the results obtained with total nodal radiation therapy. However, the relapse rate and the necessity for repeated courses of therapy is greater for those patients treated with small fields.[22]

We have selected a compromise of these approaches making use of the staging evaluation as recommended by Beretta and co-workers[15] and selecting radiation therapy fields that yield extended field irradiation, good survival and the least damage to normal tissues.

For good risk stage IA patients (nodular sclerosis and lymphocyte predominant) mantle field irradiation giving 4,000 rads in four to five weeks appears to be adequate therapy. For poor risk histologies (mixed cellularity and lymphocyte depletion) as well as all stage II patients, we use subtotal nodal radiation utilizing the mantle field followed by para-aortic nodal and splenic hilar irradiation to the same dosage. For stage IIIA patients total nodal radiation remains our standard approach although we are carefully evaluating studies utilizing less aggressive radiotherapy for abdominal disease confined to the spleen as well as subtotal nodal radiotherapy followed by chemotherapy for disease confined to the upper abdomen.

Chemotherapy

For those patients with stage IIIB and IV disease, there is little question that radiation therapy

is not adequate therapy. There is now a ten-year experience with the combination chemotherapy regimen of MOPP, developed at the National Cancer Institute.[23,24] At this time 194 patients have been treated. Of these, 94 percent were stage III or IV. The complete response rate was 81 percent and this has been duplicated by many others, including workers at our own institution. Only 22 of these patients did not have B symptoms. Within this asymptomatic group the response rate was 100 percent and there have been no relapses at the ten-year mark. For patients with B symptoms, the response rate is significantly lower (77 percent), but good. Overall, two thirds of those patients with complete remission appear free of disease at both the five- and ten-year evaluations. The nodular sclerosing histology has a significantly worse disease-free interval but similar survival.

Maintenance chemotherapy is not of any benefit provided complete remission is well-documented by rigorous restaging. In general, studies of maintenance chemotherapy have shown no improvement in survival and increased morbidity and mortality because of drug toxicity and bone marrow damage with resulting infectious complications.[25,26]

For those patients in whom a complete remission is achieved with MOPP and in whom remission is sustained for more than one year, the chance of responding to MOPP again and sustaining remission is greater than 50 percent and this is the therapy of choice.[27] However, if the patient relapses while receiving MOPP, or within one year after complete remission is achieved with MOPP, the chance of reinducing remission with MOPP is less than 20 percent and alternative therapy is indicated.

There are now alternative combination chemotherapy regimens which are useful for treating MOPP-resistant patients. The most widely used is that of Bonadonna which includes doxorubicin hydrochloride (Adriamycin®), bleomycin, vinblastine sulfate (Velban®) and imidazole carboxamide (ABVD).[28] These are all agents with activity as single agents in Hodgkin disease. In MOPP failures a complete remission rate approaching that of MOPP is obtained. A variation of the Bonadonna regimen, B-DOPA, also gives complete remission rates which are quite satisfactory in patients failing MOPP chemotherapy.[29]

A less aggressive regimen, not associated with as severe nausea and vomiting, is that employing 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), doxorubicin hydrochloride and vinblastine sulfate with and without bleomycin.[6] Here, the complete remission rate is roughly 50 to 60 percent. Another regimen, combining bleomycin, vinblastine sulfate, doxorubicin hydrochloride and streptozotocin (a nitrosourea with bone marrow sparing properties) has also yielded a 50 percent complete remission rate in a small group of patients resistant to MOPP chemotherapy.[30]

In addition to these studies with alternative chemotherapy, several studies are being carried out comparing radiation therapy alone with radiation therapy plus chemotherapy. The longest follow-up is available from the data generated at Stanford. This study compares extended field radiation therapy alone to extended field radiation therapy followed by six cycles of MOPP or nitrogen mustard, vincristine (Oncovin®) and procarbazine (MOP).[31,32] The study is now eight years old. There is no significant difference in survival between the two regimens even when analyzed by stage and histologic category. However, there continues to be significant improvement in the disease-free interval in those patients receiving radiation therapy followed by chemotherapy as compared with those treated with radiation therapy alone. O'Connell and associates have essentially repeated this study using total nodal radiation for all stages with and without six cycles of MOPP. They have also achieved similar results—that is, no difference in survival but improvement in disease-free interval with the addition of chemotherapy.[36]

The ability to give effective therapy to patients who relapse after receiving radiation therapy alone is obviously good, as pointed out by the survival figures from these two studies.[32,36] In addition, there are increasing reports of second malignancies, particularly acute leukemia, in patients treated for Hodgkin disease.[33-35] The incidence of leukemia appears to correlate with the amount of therapy delivered and seems to be highest in those receiving combination radiotherapy and chemotherapy. With these points in mind our recommendation is to use radiation therapy alone for stages IA through IIIA regardless of histology. Chemotherapy can then be used selectively for the minority of patients in whom there develops extranodal disease not identified initially, or who relapse, or in whom there is persistence of disease in an irradiated field.

Because of the striking results achieved in pa-

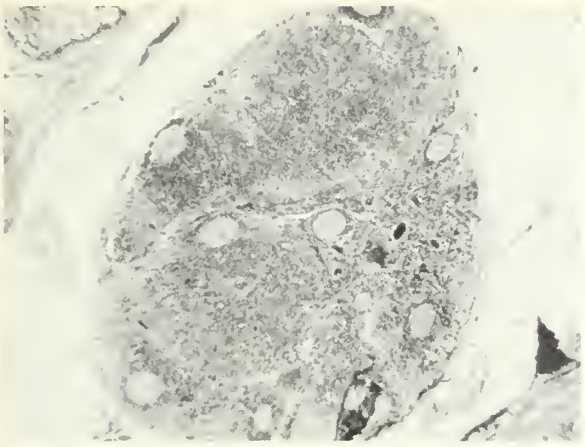

Figure 4.—Splenic hilar lymph node showing involvement of T-cell dependent area by Hodgkin disease and intact B-cell dependent follicles (reduced from ×22). (Reproduced by permission from *Cancer*.[2])

tients without symptoms in the MOPP chemotherapy regimen, the British National Lymphoma Investigation has compared the results of total nodal radiation with MOPP chemotherapy in stage IIIA patients. The study is a well designed prospective randomized trial.[37] Preliminary reports would suggest that MOPP is inferior to radiotherapy in inducing a complete remission and sustaining that complete remission. Chemotherapists have criticized this study because the MOPP de-escalation doses are significantly more conservative than in the original study where 25 percent of the dose of nitrogen mustard and procarbazine was given even when the leukocyte count was 1,000 to 2,000 per cu mm.

There are also studies being done for more advanced stages, IIIB and IV, comparing chemotherapy and chemotherapy followed by radiation therapy to areas of previous bulky disease,[38] as well as MOPP plus radiotherapy versus ABVD plus radiotherapy.[39] Although there are no significant differences at this time, these studies are only two to three years old, and there is a suggestion that adjuvant radiation therapy may have some merit and that there is no significant difference between the results obtained with MOPP or ABVD when coupled with radiation therapy.

In conclusion, then, it can be said that with our current approach to therapy, one could expect to duplicate the results reported by Kaplan and Rosenberg in more than 500 patients.[6] They used total nodal radiation therapy for all stages I through IIIA, total nodal radiation therapy with either hepatic irradiation or six cycles of MOP for stage IIIB, and MOPP with and without adjuvant radiation therapy as felt to be necessary for stage IV. An 81 percent five-year survival and a 61 percent relapse-free survival was obtained overall. The survival in stage I through III disease was very good. The survival in late stage patients was inferior to that reported with MOPP alone. In our own institution, 131 patients have been treated in the past ten years; the 10-year survival is 55 percent and the five-year survival is 65 percent; formerly more conservative staging techniques and smaller radiation therapy fields were used.[40]

Characterization of the Hodgkin Cell

Physicians have known for many years that patients with Hodgkin disease have an increased susceptibility to herpes zoster-varicella infections.[41] More recently, it has been shown that these same patients have decreased levels of measurable T-cells by E-rosette measurement, and that they have normal levels of T-cells by cytotoxicity assay.[42] In addition, skin test reactivity and E-rosetting can be restored toward normal by giving levamisol.[43] Another observation, pointed out by Kadin, has been the occurrence of Hodgkin disease in T-cell dependent areas of some patients' lymph nodes with residual intact normal follicular areas, the B-cell area (Figure 4).[2] For these reasons Order and Hellman have hypothesized that Hodgkin disease arises as a T-cell defect associated with virally infected T-lymphocytes.[44]

On the other hand, Lukes and co-workers have observed Reed-Sternberg-like cells in infectious mononucleosis[45] and similar cells have also been reported in angioimmunoblastic lymphadenopathy,[46] two disorders which are B-lymphocytoid in nature. In addition, Leech has shown intracytoplasmic immunoglobulin in Reed-Sternberg cells, a characteristic of the B-lymphocyte.[47] Recently, from Lukes' laboratory, composite transmission electronmicrographs of normal B-lymphocytes, pokeweed-mitogen-stimulated B-lymphocytes, atypical mononuclear cells from nodular sclerosing Hodgkin disease, and classifiable lacunar cells from nodular sclerosing Hodgkin disease have been used to support the hypothesis of a B-lymphocyte transformation as the origin of the Hodgkin cell.[48]

However, for many years morphologists such as Rappaport have stated that the Reed-Sternberg cell is a malignant histiocyte based on morphologic grounds alone.[49] The multinuclearity is

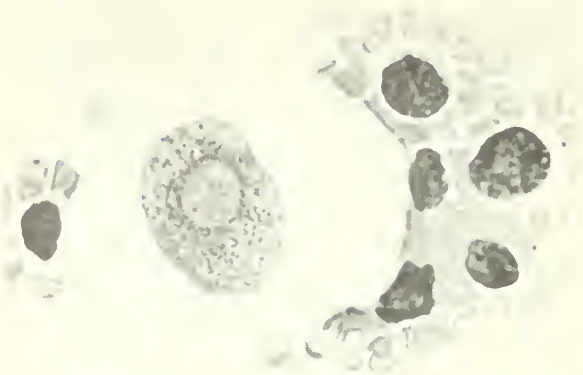

Figure 5.—Hodgkin giant cell partially surrounded by rosetted T-lymphocytes. Wright-Giemsa stain. Magnified from ×160. (Reproduced by permission from *The Lancet*.[51])

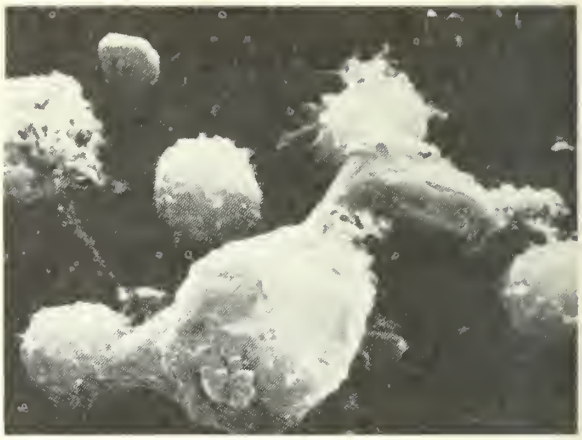

Figure 6.—Scanning electron microscopy showing cytoplasmic bridging between Hodgkin giant cell and surrounding T-lymphocytes (reduced from ×3600). (Reproduced by permission from *The Lancet*.[52])

atypical but the size, nuclear/cytoplasmic ratio, and hematoxylin and eosin staining characteristics are quite reminiscent.

The study of this cell has been extremely difficult because of its sparse occurrence within involved tissues and the necessity for working with sterile, viable tissue. In addition, the occurrence of the cell in the presence of a pleomorphic infiltrate has made its concentration and selection for study difficult. Kadin, Gold, Stites and I undertook this project beginning in 1974. We made use of a velocity sedimentation technique to eliminate the small lymphocytes and concentrate the large, mononuclear and binuclear Hodgkin cells.[50] We found that they were always surrounded by normal-appearing small lymphocytes which were closely adherent.

We had previously been able to characterize malignant cells using the E-rosette test in acute lymphoblastic leukemia and applied this technique to Reed-Sternberg cells. We saw no evidence of T-lymphocyte properties on the cells themselves. However, about 95 percent of the small lymphocytes surrounding the cell were T-lymphocytes by this criterion (Figure 5). Stites confirmed this observation using rabbit anti-human thymocyte serum and indirect immunofluorescence. Fluorescence of the small, adherent lymphocytes was shown. No fluorescence was shown on the membrane or within the cytoplasm of the Reed-Sternberg cells.[51]

Scanning electron microscopy showed that the surrounding T-cells were closely adherent and that there were cytoplasmic bridges between the surrounding lymphocytes and the Hodgkin cells (Figure 6).[52] We have speculated that perhaps this is a manifestation of a good immunologic response although normal histiocytes and lymphocytes have shown similar interaction.[53,54]

Kadin had also been able to show monoclonal immunoglobulin within the cytoplasm of malignant B-lymphocytes such as multiple myeloma cells, and that the immunoglobulin was similar in nature to the monoclonal protein spike in the serum electrophoresis. As with Leech,[47] we were able to show intracytoplasmic immunoglobulin within the Hodgkin cells. However, we were unable to show any Hodgkin cells with definable surface immunoglobulin. This study also confirmed our initial conclusion that the cell was surrounded by T-lymphocytes and not by B-lymphocytes (Figure 7).

Recently Reed-Sternberg cells in frozen section have been proved to have complement receptors.[55] This study utilized sheep red blood cells coated with immunoglobulin (IgM) and complement. This observation has been substantiated by Kaplan who has also documented that the complement receptor on this cell is specific for C_{3b} and that when C_{3b} is inactivated to C_{3d} there is no rosetting.[56] This specificity for C_{3b} has been shown to be characteristic of the receptor on the monocyte-histiocyte.[57] The B-lymphocyte has a complement receptor for both C_{3b} and C_{3d}.

Billing has recently prepared an antiserum that is apparently similar to the anti-leukemia serum of Halterman and co-workers.[58,59] This antiserum labels the myeloblasts and lymphoblasts of acute leukemia,[60] the B-lymphocytes of lymphocytic lymphoma, and normal monocytes and histio-

cytes. It does not label normal or malignant plasma cells, the mesenchymal cells seen in pleural effusions, or solid tumor cell suspensions (lung cancer, colon carcinoma, breast cancer, for example). Positive labeling of the binucleate Reed-Sternberg cell further confirms the histiocyte-macrophage or B-lymphocyte origin of this cell.

Preparations of Reed-Sternberg cells in our laboratory confirm previous observations that the Hodgkin cell does not contain nonspecific esterase.[61,62] Positive nonspecific esterase staining is characteristic of monocytes and histiocytes.[63]

Phagocytosis studies with staphylococci and zymosan particles have always been negative in our laboratory. However, Kaplan has recently reported the slow phagocytosis of India ink by Hodgkin cells in short-term tissue culture suggesting a macrophage-histiocyte property.[56]

Scanning electron microscopy has also added confusion to the evaluation of the Hodgkin cell. In the preparations from our laboratory, one can appreciate the ruffles on the Hodgkin cell surrounded by the smooth T-lymphocytes and the similar surface characteristics seen on a normal histiocyte-macrophage (Figure 8). In addition, Figure 9 shows a binucleate Reed-Sternberg cell containing a phagocytosed lymphocyte.

In summary, then, one can state that conclusions regarding the origin of the Hodgkin cell are still not possible. The surface properties and lethargic phagocytosis are most reminiscent of the monocyte-histiocyte cell series. On the other hand, intracytoplasmic immunoglobulin is not characteristic of this cell series but more consistent with a B-lymphocyte origin. Experiments have been completed to determine the origin of the cytoplasmic immunoglobulin—that is, exogenous or endogenous to the Hodgkin cell—and findings will be published shortly. This observation should clarify the true nature of the cell and provide new approaches to the identification of unsuspected, residual, microscopic disease and, perhaps, new therapeutic tools.

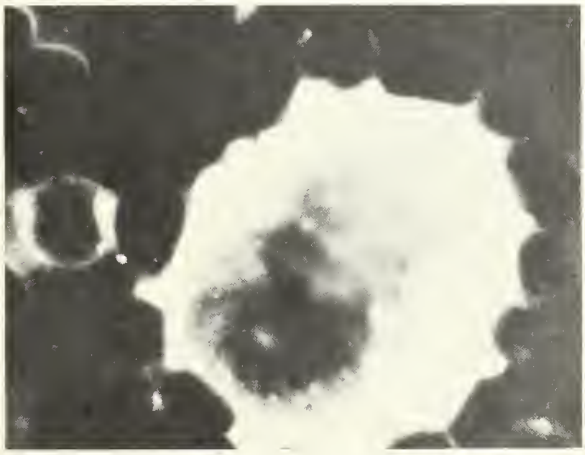

Figure 7.—Reed-Sternberg cell showing intracellular immunoglobulin identified by fluorescein-labeled rabbit anti-human IgG antiserum (Meloy). Surrounding T-lymphocytes are not labeled. Labeled B-lymphocytes can be identified in the surrounding cellular matrix (×1000). (Courtesy of M. Kadin, MD, Dept. of Path. and Lab. Med., University of Washington.)

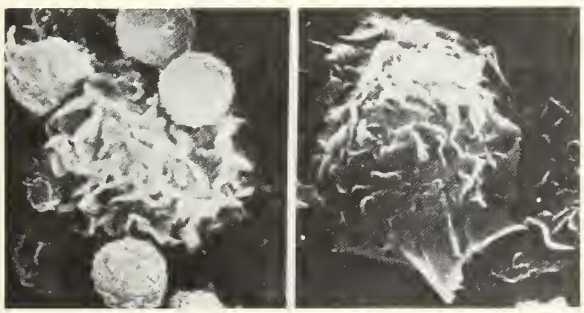

Figure 8.—**Left,** Hodgkin cell showing surface ruffles (lamellae) and surrounding smooth T-lymphocytes (reduced from ×3770), and **Right,** normal peritoneal macrophage (reduced from ×4330). (Reproduced by permission from *The Lancet.*[62])

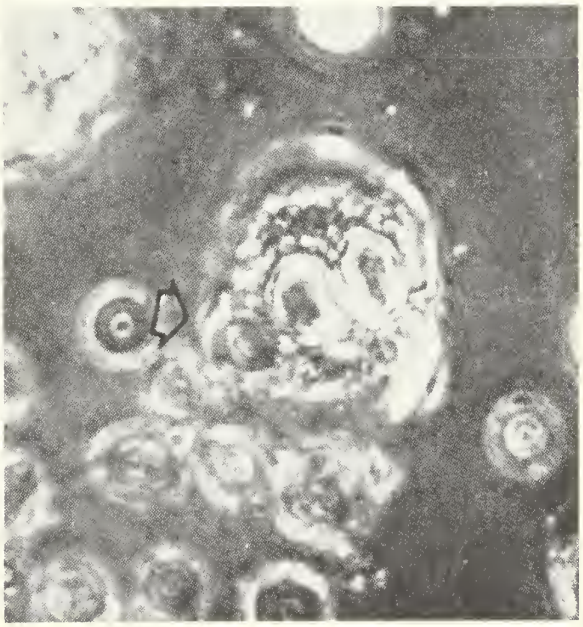

Figure 9.—Binucleate Reed-Sternberg cell seen by phase-contrast microscopy with phagocytosed lymphocyte appearing on the same focal plane as Reed-Sternberg nuclei (magnified from ×1000). (Reproduced by permission from *The Lancet.*[62])

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Important Advances in Clinical Medicine

Epitomes of Progress—General and Family Practice

The Scientific Board of the California Medical Association presents the following inventory of items of progress in general and family practice. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in general and family practice which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General and Family Practice of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

A Little More Attention to Parasites

INTESTINAL PARASITIC INFESTATION is one of the most common human afflictions. It is often considered a rarity in the United States. However, some communities in Southern California close to Mexico have a high incidence of infestation, as do communities with recent influxes of Southeast Asian immigrants.

Symptoms indicative of possible parasitic infestation include poor nutritional status, vague or acute abdominal pain, indigestion, nausea, vomiting, fatigue, poor appetite, constipation, diarrhea, gastrointestinal bleeding, headache, chronic cough and asthma-like conditions, and lag in growth and maturation in children. Generally, poor sanitation and personal hygiene, increasing international travel, contact with domestic animals, and some group activities are well known factors in its spread.

In general, studies of stool specimens on three separate dates are required both before and after treatment. If results in one member of the family are positive, examinations should be carried out in the entire family. Findings other than positive stool studies include anemia and eosinophilia, especially in cases involving pathogenic parasites. Needless to say, care and thoroughness are essential in all examinations.

Common parasites include Ascaris lumbricoides, Enterobius vermicularis, hookworms, Trichiuris trichiura, Giardia lamblia, Entameba histolytica, Strongyloides stercoralis and Hymenolepis nana. Taenia saginata, Schistosoma mansoni and Dientamoeba fragilis also are not uncommon. Not surprisingly, many patients have been found to be infested with more than one parasite, combinations of two or more of the above mentioned pathogenic ones or of other nonpathogenic ones. In multiple infestation involving Ascaris, treatment should first be directed against this parasite; mebendazole (Vermox®) is often very effective. Mebendazole is relatively safe and is effective for pinworms, hookworms and whipworms. It is, however, not recommended for childern less than 3 years old. Other effective regimens include pyrontel pamoate (Antiminth®) or piperazine for Ascaris; Antiminth or pyrvinium pamoate (Povan®) for pinworms; Antiminth or thiabendazole

(Mintezole®) for hookworms; Mintezole for whipworms and S. stercoralis; metronidazole (Flagyl®) for E. histolytica and giardiasis; niclosamide (Yomesn®) for tapeworms, and stibophen (Fuafuadin®) or niridazole (Ambihar®) for schistosomiasis. Sometimes repeated therapy is necessary. For pinworms, simultaneous therapy of all the family or group members is necessary as well as a repeated treatment two weeks after the initial treatment.

Often, the need for active treatment in parasitic infestation is relative, and withholding treatment in asymptomatic cases is recommended because many are self-limiting. However, it should be noted also that symptoms often fluctuate, varying from a very severe condition which leads patients to seek medical attention to a completely asymptomatic one. In children, such a fluctuating and insidious course may disturb and delay schooling and social activities. Those children often have multiple infestation, high eosinophile counts and past history of symptoms and signs. It is especially in those circumstances that the treatment of a seemingly self-limiting or relatively asymptomatic infestation should be given serious consideration. Also, we strongly believe that at least in certain communities and locations every practicing physician should keep abreast of the problem of parasitic infestation and its eradication as an integral part of medical practice.

MYUNG MI RYU, MD

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Graphic Analysis of Obstetric Labor

THE DIAGNOSIS of prolonged labor using only elapsed time involves the difficulty that some serious labor observations may be overlooked by such a coarse criterion. Whereas some normally progressive and uncomplicated labors may last longer than defined time limits, some ominous labor patterns are potentially so hazardous that they should be recognized well before any such time limit is reached. One study has shown that 10 percent of all labors under 20 hours considered normal clinically were abnormal when progress of labor was plotted graphically, and that almost 50 percent of patients diagnosed as having abnormal clinical labor had normal patterns of cervical dilatation. In order to provide a more objective method to better monitor labor, Friedman has developed a simple method of graphically displaying the progress of labor judged by time, cervical dilatation and station of the presenting part.

This method records observations that the physician obtains in any event and plots these observations on square-ruled graph paper with hours of labor as horizontal coordinates, cervical dilatation as vertical coordinates on the left, and station of descent as vertical coordinates on the right. The method is simple to apply in everyday obstetric practice and is fully described in the references listed.

Six major disorders of labor are readily characterized by use of this method. These can be grouped in three categories: (1) *prolonged latent phase;* (2) *protraction disorders:* (a) protracted active-phase dilatation and (b) protracted descent, and (3) *arrest disorders:* (a) prolonged deceleration phase, (b) secondary arrest of dilatation and (c) arrest of descent. Each of these disorders can be further related to cause, response to treatment, and prognosis. Each disorder involves its own preferred approach to management. In general, therapeutic rest is indicated for prolonged latent phase; support and expectancy are preferred for protraction disorders; cesarean section is indicated in arrest disorders complicated by disproportion, and oxytocin stimulation is reserved for arrest disorders occurring without disproportion.

Use of the graphic analytic technique adds an important new dimension to the diagnostic and therapeutic capabilities of physicians caring for obstetric patients in labor. This method is recommended for application in everyday practice and allows for improved teaching and learning in residency training programs.

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Friedman EA: Patterns of labor as indicators of risk. Clin Obstet Gynecol 16:172-183, Mar 1973

Endometrial Sampling

RECENTLY THERE HAS BEEN a plethora of reports indicating increased incidence of endometrial cancer in patients receiving estrogen therapy. The need for a simple and accurate method of endometrial sampling has become apparent. Since 1943

various techniques have been used to obtain endometrial tissue for diagnosis, including aspiration, jet-washing and endometrial biopsy studies. Since the classical method—dilatation and curettage—requires admission to hospital, general anesthesia and considerable cost to the patient, clinicians have been anxious to find a reliable office procedure to obtain endometrial tissue in the evaluation of abnormal bleeding or for endometrial dating. Curently the jet-washing technique as described by Gravlee and the suction endometrial biopsy as described by Novak are the most popular.

It seems that, overall, endometrial biopsy study is a superior technique. Jet-washing is simple and very well tolerated by patients without anesthesia. Statistically, however, there is a larger percentage of missed endometrial carcinoma (9 percent) than with endometrial biopsy (7.9 percent). In addition, the jet-washing technique is consistently less accurate than endometrial biopsy in the diagnosis of adenomatous hyperplasia and in endometrial dating. Both techniques have a 12 to 16 percent incidence of obtaining insufficient tissue for diagnosis. Therefore, even though the suction biopsy technique is slightly more uncomfortable to the patient, it seems to be superior.

Currently, there is a variant technique of endometrial biopsy using vacuum aspiration as described by Vabra. After extensive clinical trials in Europe, it seems to be slightly more accurate than the routine suction biopsy and significantly more effective as a therapeutic modality in evacuation of uterine tissue.

Since both suction biopsy and jet-washings have a substantial incidence of obtaining insufficient tissue for diagnosis of endometrial cancer, a negative or inconclusive result should not be relied upon. For this reason, many clinicians are returning to dilatation and curettage as the primary procedure. In an outpatient setting, dilatation and curettage can be done under paracervical block anesthesia with reduced expense to the patient and the security that a second procedure will not be necessary.

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Hypertension in Children and Adolescents

HYPERTENSION has generally been considered an adult problem, and little attention has been focused on the incidence of this disorder in either children or adolescents. The recording of blood pressure as a routine part of a physical examination may be viewed as less important during childhood or adolescence than in later years. Information concerning the mechanisms, end points and therapy of essential hypertension has been developed from studies of adult populations, so that little is known about this entity in young people. Recently, however, two developments have taken place which should increase our concern about hypertension in children and adolescents: (1) observations that the siblings of adults with known essential hypertension, regardless of their age, are more likely to have elevated blood pressure levels than the general population and (2) hypertension in adolescents is being discovered more frequently through community blood pressure screening programs.

Primary hypertension in children is rare; secondary causes of hypertension in childhood usually involve abnormalities of renal development and function, but may include coarctation of the aorta, adrenal tumors and disorders of the central nervous system. The incidence of primary hypertension in adolescents is unknown, although it is probably more frequent than hitherto suspected. A search for remedial causes of hypertension in adolescents with elevated blood pressure still is indicated.

The flush technique may be used to record blood pressure in infants. Blood pressure measurements should be a routine part of physical examinations in every child more than 2 years old. The blood pressure cuff must be carefully selected in order to obtain accurate readings. The inner rubber bag should be wide enough to cover two thirds of the length of the arm and three quarters of the circumference of the upper arm or thigh while leaving the antecubital or popliteal fossa free.

There are no major differences in blood pressure levels between boys and girls of the same age. Although precise information concerning the normal range of blood pressure in children and teenagers is not available, the figures shown in Table 1 for the 95th percentile for systolic and diastolic pressures serve as an adequate guide to unsafe levels for any age.

TABLE 1.—*95th Percentile Values for Blood Pressure By Age*

Age	*Systolic Pressure (mm of Mercury)*	*Diastolic Pressure (mm of Mercury)*
0-6 months	110	60
3 years	112	80
5 years	115	84
10 years	130	92
15 years	138	95

Family physicians have both the responsibility and opportunity to contribute to the early diagnosis and appropriate management of hypertension in children and adolescents. Careful follow-up of single observations of elevated blood pressure is required to avoid misdiagnosis of hypertension or to facilitate definitive therapy when indicated.

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Clinical Uses of Ultrasound in Diagnosis

SINCE THE ADVENT of sonar in the 1940's, advances in ultrasound have made it increasingly valuable in therapeutic and diagnostic medicine. Diagnostic approaches with ultrasound have been refined with increased knowledge and understanding of the various methods of information display as well as development of a variety of transducers.

In studies of the head, the most common procedure is echoencephalography—localization of the midline of the brain. The midline structures are identified and considered abnormal if there is more than a 3 mm shift. Tumors or subdural hematomas cannot be identified, but can be inferred, suspected or followed by electroencephalograms. The condition of hydrocephalic patients can be followed because echoes can be adjusted to determine the size of the lateral ventricles.

Special transducers have been developed to reflect echoes from the retina, choroid and sclera of the eye. Intraocular and retrabulbar lesions can be differentiated even if the lens is opaque. Fluid in the paranasal sinuses can be detected with ultrasound. Methods of evaluating thyroid masses and cysts as well as thyroglossal cysts are being developed. Laryngeal movement also is under the scrutiny of some ultrasound specialists.

A most important and relatively simple use is found in gynecology and obstetrics. Ultrasound can be used to verify the diagnosis of multiple gestations, hydatidiform mole, fetal demise, cephalo-pelvic disproportion, fetal maturity, fetal presentation, and accurate biparietal measurements in a breech presentation or obese mother. Anencephaly and hydrocephaly are two anomalies that can be accurately diagnosed. Ectopic pregnancy and solid or cystic lesions of the tubes or ovaries can be differentiated. The placenta can be accurately located in case of suspected placenta previa. The Doppler ultrasound equipment converts the fetal heart tones to audible sounds and is auscultated with a stethescope as early as ten-weeks' gestation. The placenta also can be located, but the technique is best used with the aid of B scan ultrasound in such instances.

Abdominal masses are frequently a puzzle even after other studies are completed. Ultrasound can be used to identify cystic, solid and retroperitoneal masses anywhere in the abdomen. The presence of pancreatic as well as hepatic and splenic tumors and vascular anomalies can be determined. A radiographic nonfunctioning gall bladder often is found with ultrasound to have cholelithiasis; therefore, the risk of unnecessary laparotomy is reduced. Second dose cholecystography also can be avoided in allergic patients. In cases of abdominal masses in pediatric patients ultrasound probably should be used because it is noninvasive and may meet less patient resistance than a painful, invasive procedure. Cystic or solid renal masses are simply differentiated. Even complex renal masses yield useful information when ultrasound is used. Free fluid in the abdomen can be easily differentiated.

Thoracic ultrasound is less useful because the sound waves do not transcend air. The fascinating field of echocardiography makes ultrasound a valuable tool in the diagnosis of cardiovascular disease. Other thoracic diseases identifiable with ultrasound include pleural effusion, pulmonary infarction and pulmonary embolism. Vascular lesions such as aneurysms of the abdominal aorta and, under special conditions, thoracic aorta are located and measured with a high degree of accuracy, even to the extent that dissection of the aneurysm can be determined if the approach is nearly or completely perpendicular to the dis-

sected wall. The Doppler method of examination is used to determine stenosis of the aorta and other vessels, even into the pedal arteries, and is more reliable than palpation.

With the advent of computerized tomography, it is possible that some uses of ultrasound will be of less value, especially in the thorax and head. However, it must be remembered that ultrasound has no known contraindications and is nonionizing.

Computerized tomography makes use of irradiation that may be injurious if used extensively. In testing animals with significant exposure to ultrasound, tissue damage to neural, cutaneous or other systems has not been found. Heat is produced by ultrasound when intensity levels are greater than 1 watt of electrical energy per square centimeter of crystal surface. Diagnostic B mode energy levels range between 0.04 and 0.004 watts per square centimeter of crystal surface.

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Treatment of Croup

CROUP, A COMMON SYNDROME of respiratory stridor, cough and hoarseness due to varying degrees of laryngeal obstruction, frequently presents a therapeutic challenge to family physicians. The mainstays of treatment for years have included adequate hydration, humidification, careful sedation when needed, and use of oxygen or even tracheostomy in severe cases of laryngeal obstruction. Antibiotics and steroids have no value in this viral disease. The use of intermittent positive pressure breathing (IPPB) with nebulized racemic epinephrine has recently become accepted as an important adjunct to therapy which can provide dramatic symptomatic relief in the acute case and potentially decrease the need for admission to hospital and tracheostomy if its limitations are recognized.

At first this method was used in the most severe cases of croup, but is now also found useful in the mild or moderately severe case. The method involves the use of a positive pressure respirator with a face mask for 15 minutes using a nebulized solution of 2.5 percent racemic epinephrine diluted 1:8 with water. If the response is not satisfactory or if symptoms recur, additional treatments can be given. This treatment is well suited to use in emergency rooms, but must be followed by an adequate period of observation before a patient is sent home.

While all reported studies have shown the acute beneficial results of IPPB with nebulized racemic epinephrine in the treatment of croup, it is still unclear whether the important element in this treatment is the IPPB or the use of nebulized racemic epinephrine. Some reports have shown there to be a decrease in the incidence of both hospital admissions and tracheostomy through use of this treatment, while other studies have not reported such positive outcomes.

Although IPPB with nebulized racemic epinephrine can be recommended as an important addition to the treatment of croup, two precautions must be heeded: (1) the diagnosis must be accurate because IPPB is not effective in epiglottitis and may delay appropriate urgent treatment and (2) an adequate period of observation must follow the use of IPPB because symptoms often recur within two hours even when the initial response to treatment has been satisfactory.

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New Hope for Patients With Psoriasis

THERE IS NEW HOPE for patients suffering from psoriasis. Although the cause of psoriasis is not known, much has been learned about the pathophysiology of the disease and the response to chemical and physical methods of therapy. Psoriasis may be present as a cosmetic nuisance or a disabling, crippling, destructive, socially ruinous disease—or any degree of severity between these two extremes.

Recognition that the underlying process that results in the thickened plaques of skin associated with psoriasis is the result of increased rate of replication of the epidermal cells led to a recent

rationale of therapy. The turnover time in the production of normal epidermis is 28 days. The turnover time in psoriasis is three to four days. This accounts for the dramatic growth and thickening of the skin.

Methyltrexate, an antimetabolic dioxyribonucleic acid (DNA) inhibitor used effectively in the treatment of choriocarcinoma was found to be very effective in the treatment of psoriasis. This is an exceedingly potent and dangerous chemotherapeutic agent, the use of which can be justified only in severe cases of generalized psoriasis. Its use should be limited to oncologists or dermatologists familiar with the agent and capable of closely monitoring changes in the liver, bone marrow and kidneys. The benefit-to-risk ratio is unfavorable except in very unusual cases.

A new method of treatment used by several investigators appears very promising. Historically it was noted that in travelers afflicted with psoriasis there was an especially beneficial effect when they visited the region of the Dead Sea. It was reasoned that the good results may have accrued from the type of light penetrating the extra thickness of the atmosphere. Indeed, there was found to be a longer wave length in the ultraviolet spectrum, the shorter wave length having been filtered out. It was observed that certain chemicals (psoralens) used in the treatment of viteligo in India and Egypt as long ago as 2,000 years, also had a beneficial effect on psoriasis in some instances.

The combined use of the longwave (UV-A 320 to 400 nm) light and methoxsalen (8 methoxypsoralen) or trioxsalen (4, 5′, 8 trimethyl-psoralen) produced remission of the psoriatic lesions. Methoxsalen, the more commonly used psoralen increases photosensitivity in the skin and increased pigmentation in the presence of ultraviolet light. The photo-excited psoralen molecules bind to the DNA molecule in a manner to inhibit its replication. This effect is most pronounced in the presence of longwave UV-A (320 to 400 nm). The shortwave UV-B (275 to 320 nm) is relatively ineffective. The most effective use of methoxsalen is by oral administration. Topical use is unsatisfactory because of difficulty in controlling dosage. Severe cases of photosensitivity often result in blistering and irregular disfiguring hyperpigmentation of the skin. Topically and intraperitoneally, methoxsalen and longwave or conventional ultraviolet light have produced squamous cell carcinoma in animal studies.

Methoxsalen administered orally has not been shown to potentiate carcinogenesis or hepatotoxicity in human subjects in a study extending over 20 years. Methoxsalen, therefore, appears to be a safe drug, which, if administration is followed by exposure to longwave UV-A (320 to 400 nm), is effective in causing the remisison of psoriatic lesions. Careful dosage and careful exposure of measured amounts of irradiation are essential to the success of this method of treatment.

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Nonsteroid Anti-inflammatory Agent for Treatment of Rheumatoid Arthritis

AMONG A NUMBER of new agents recently placed on the market for treatment of arthritis, tolmetin sodium (Tolectin®) possesses anti-inflammatory analgesic and antipyretic activity. While the exact mechanism of action is unknown, this new nonsteroidal anti-inflammatory drug is useful as an adjunct to the treatment of rheumatoid arthritis, particularly in patients who are sensitive to aspirin. This medication comes in a dosage strength of 200 mg and the recommended dose is 1,200 to 2,000 mg a day in divided doses taken with food to avoid gastric irritation that can be a problem with this drug. Double-blind cross-over studies have been made and findings indicate that in recommended doses tolmetin is as effective as aspirin and indomethacin. Tolmetin sodium is indicated for the relief of signs and symptoms of rheumatoid arthritis in acute flare-ups and also in long-term management of the chronic disease.

Guidelines for gauging improvement with use of this medication have been a reduction in swelling and pain, a reduction of the number of involved joints, a reduction of the duration of morning stiffness, or a decrease in disease activity and improved functional capacity. While this drug has been noted to be equal to indomethacin and aspirin in controlling disease activity, the frequency of gastrointestinal adverse effects and tinnitus was definitely less than those of patients treated with aspirin, and the incidence of central nervous system adverse effects was less than with the indomethacin treated patients.

Contraindications to this medication are a direct sensitivity to the medication and a possible cross-sensitivity to other nonsteroidal inflammatory drugs. Caution should be observed in any patient with gastrointestinal symptoms and a past history of peptic ulcer or gastrointestinal bleeding, and this should be a reason for withdrawal of medication. There has been some fluid retention with the use of tolmetin sodium. The metabolites of this drug have been found to give a positive test for proteinuria utilizing sulfasalicylic acid, with no interference in tests for this urinary constituent using dye-impregnated commercial strips, or urine sticks. Use of this medication during pregnancy and in nursing mothers is not advised. The drug interactions have been few even though tolmetin sodium does extensively bind to plasma protein.

This drug can be used in conjunction with other treatments. Conjoint use with acetaminophen, gold, and steroids has been carried out. It is suggested that tolmetin sodium is an adjunct for the treatment of severe cases of rheumatoid arthritis. Studies also have indicated that in a number of patients there was an effective response to this medication. These responses cannot be predicted before its use; therefore, tolmetin sodium may be used if a substitute or an adjunct to therapy in patients with severe rheumatoid arthritis is needed.

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Newer Nonsteroidal Anti-Inflammatory Compounds

FEW ARTHRITIC PATIENTS can be cured, but most who suffer from the arthritides need not become prostrate cripples. Unfortunately, the key element that sets off the chain of events leading to synovitis is unknown. Until there is a better understanding of what triggers the disease, physicians cannot hope to intervene much earlier, and must be content with small improvements in treatment.

Family physicians, therefore, are put in the position of attempting to estimate minor benefits of new anti-inflammatory drugs. However, even small degrees of improvement are welcomed by patients.

The most common drugs now available to family physicians are nonsteroidal anti-inflammatory agents such as talmetin, naproxin, fenaprofin calcium and ibuprofin. These drugs do add depth to the arthritis armamentarium. They all appear to be as effective as aspirin, but have fewer harmful side effects.

Naproxin (Naprosyn®) is an arylalkanoic acid derivative that has considerable promise in the treatment of arthritis. It has been widely tested in clinical trials. In the dosage of 250 mg twice a day it is comparable to aspirin and indomethacin but is tolerated better than either of these agents. Combination therapy using naproxin has been shown to be more effective than aspirin alone.

The mode of action of ibuprofin (Motrin®) in inflammation is unknown. It is an analgesic with nonsteroidal anti-inflammatory activity. It has been shown to have a suppressive mechanism of action on mediators of inflammation (such as decreasing prostaglandin synthesis) similar to indomethacin. One paper reports ketoprofin to be better tolerated than ibuprofin and at least as efficacious. Ibuprofin's significant anti-inflammatory activity appears to be effective only in the upper end of the range of 900 to 2,400 mg per day. Antiarthritic activity of the drug in lower dosages probably reflects a primary analgesic and perhaps an antipyretic effect rather than suppression of inflammation.

Fenoprofin calcium (Nalfon®) is another proprionic acid derivative, but its safety and effectiveness have not been established in rheumatic arthritic patients who are designated by the American Rheumatism Association as Functional Class IV (largely or wholly incapacitated with the patient bedridden or confined to a wheelchair permitting little or no self-care).

Talmetin (Tolectin®) is an effective and safe anti-inflammatory agent. In addition, it appears to be less toxic to the liver than even aspirin. In the case of juvenile rheumatoid arthritis, results of liver function tests improved during its administration and, again, it appeared to be as effective as aspirin in the short-term management of juvenile rheumatoid arthritis.

Scientific literature on arthritis practically ignores the recent excitement over hormonal therapy of rheumatoid arthritis. High blood levels of estro-

gen and progesterone induced by weekly injections of these hormones paralleling the blood levels in early gestation are recommended by a few physicians but ignored by many. Family physicians should go slowly in ordering this program.

And last, a double-blind parallel trial of 42 subjects with shoulder pain showed that acupuncture was no more effective than placebo in relieving shoulder pain.

Even though considerable progress has been made in the treatment of arthritis in the last 25 years, at the therapeutic heart remains an informed and sympathetic physician.

WILFRED SNODGRASS, MD

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EDITORIALS

Communication With the FDA

WE ARE IMPRESSED with the evident sincerity of the effort of the Food and Drug Administration (FDA) to establish genuine two-way communication with practicing physicians. Commissioner Donald Kennedy's article elsewhere in this issue bears witness to this. And the fact that high officials of the FDA will be present and respond to physicians' questions and comments at a "Tell It to the FDA" session at the Annual Meeting of the California Medical Association on March 18, 1978 is further evidence of this sincerity. In recent years the FDA has become more aggressive in carrying out its legal mandate and indeed its hand has repeatedly been strengthened by the Congress. But all has not been well with the agency. There have been internal difficulties—inadequate staffing and mounds of paperwork—as well as external criticism. For reasons, some but not all of which were beyond its control, the FDA has found itself often the center of controversy and often in an adversary posture vis-a-vis the pharmaceutical industry, physicians and others, and at times even the public. Recently a two-year study of the agency's operations has been completed which concluded that "The FDA's implementation of the system of drug regulation needs substantial improvement," and Secretary Califano has indicated that this study will be the foundation for an overhaul of the agency.

Physicians are at the interface where the actions or inactions of the FDA have impact upon patients and patient care. Physicians are particularly aware that any drug which is effective is apt to have toxic properties, and whether or not to use a drug or how to use it, must be a judgmental decision as to whether the benefits to be gained outweigh the risks to a given patient in a given situation. It is for reasons such as this that physicians are distrustful of the outright banning of drugs that they believe to be useful in the proper circumstances, because of their toxicity or a remote possibility that they may produce cancer in any individual patient at some future time. And it is for reasons such as this that physicians question the wisdom of across-the-board regulations which deter them in the exercise of their professional judgment in a particular situation.

There is much to be said on all sides of these and many other aspects of the FDA's regulating activities. Commissioner Kennedy has opened a window or two and is letting some fresh air find its way into the inner sanctuary of the agency. This is not only refreshing, it is healthy. Individual physicians and the medical profession as a whole should enter into direct and candid communication with the FDA. From this will come greater understanding of the problems on the part of all concerned, and no doubt better regulations.

—MSMW

Enzymatic Diagnosis of Infarction

IN THIS ISSUE of the WESTERN JOURNAL, Guzy reviews some information available regarding the diagnosis of myocardial infarction by assessment of plasma MB CK* activity. In assessing the validity of conclusions reached based on a literature survey, it may be worthwhile to focus on some implicit considerations, particularly those bearing on some still controversial issues. Although results of laboratory tests expressed as numerical values are often considered sacrosanct, implicit limitations of the procedures themselves should be taken into account. Assay of MB CK can be accomplished with three generically different approaches: (1) qualitative assays that detect enzymatic activity, (2) quantitative assays of enzymatic activity, (3) quantitative assays that detect CK molecules rather than enzymatic activity.

The first category, exemplified by electrophoretic techniques, relies on physical separation of one isoenzyme from another in the sample, and detection of enzyme activity with the use of coupling reactions resulting in generation of dihydronicotinamide adenine dinucleotide phosphate

*The term creatine kinase (CK) (E.C.2.7.3.2) is preferred to creatine phosphokinase (CPK) by the International Union of Biochemistry Enzyme Commission. "Phosphokinase" is redundant since kinases, by definition, mediate transfer of high energy phosphate.

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(NADPH) assessed fluorometrically or reduction of redox dyes visualized directly in regions where isoenzyme activity is present on the supporting medium. Such procedures are not quantitative for a variety of reasons including asymmetric distribution of isoenzymes along the axis of the supporting medium; limitation of diffusion of substrate; loss of visualizing dye or NADPH from the medium; nonlinearity of reaction rate for one or more isoenzymes because of disparate activities of each; and variation in affinity of individual isoenzymes for substrate or reagent in the incubation medium.[1] Thus, even when loading conditions are standardized such that the same total amount of CK activity is applied to the medium, variation in the proportion contributed by each isoenzyme and intrinsic limitations of the system itself limit quantitative accuracy and precision.

The second category of approaches has been developed to obviate some of these difficulties. Again, CK isoenzymes are separated by some physical procedure such as chromatography,[2] elution from cellulose acetate membranes[3] or batch adsorption,[4] and isoenzyme activity is assayed in aqueous medium under conditions optimized for the amount of activity present. Under these conditions, kinetics can be defined and hence quantitative results obtained. On the other hand, since detection of MB CK still relies on detection of enzymatic activity, anything interfering with enzymatic activity in the sample itself or the reaction medium will lead to spurious results. For example, the presence of myokinase in the sample (elevated in plasma from patients with myocardial infarction) will lead to production of ATP and hence NADPH when the conventionally used CK enzyme reaction medium is employed resulting in apparent CK activity exceeding that due to CK itself. Conversely, inhibitors, sometimes seen in plasma samples, may interfere with the CK enzymatic reaction or with enzymatic reactions employed to couple CK activity to the production of NADPH, giving rise to falsely low estimates of CK activity in the sample.

A third approach has been developed to provide quantitative estimation of the amount of CK in a sample without relying on detection of CK enzymatic activity. Radioimmunoassay[5] permits detection of immunoreactive CK protein whether or not it retains its enzymatic activity. For example, results with a recently developed radioimmunoassay are the same whether or not a sample has been stored under conditions in which enzymatic activity of its CK has been lost by exposure to room temperature or sulfhydryl reagents.

As noted by Dr. Guzy, a great deal of useful information has been obtained with qualitative assays of MB CK enzymatic activity.[6,7] When a clinician wishes to know whether or not MB CK activity is elevated to a pronounced degree, such assays usually provide an unequivocal answer. On the other hand, modest variations in enzymatic activity within the normal range or modest elevations below the threshold for detection of the qualitative procedure employed cannot be assessed. Accordingly, if the clinician wishes to know whether or not *any* MB CK has been released into the circulation, he cannot answer the question with the use of a qualitative assay. With quantitative procedures relying on detection of enzymatic activity, sensitivity is a serious problem. Those techniques utilizing chromatographic separations lead to dilution of the sample and hence lost peaks may be unavoidable, and when MB CK activity is low, the percentage error introduced by contributions from other isoenzyme peaks may be substantial. Obviously, then, if the clinician wishes to exclude the occurrence of release of any MB CK into plasma in a particular patient, reliance on techniques in the first two categories may not be sufficient.

Unfortunately, despite conventional semantics, the question of whether or not myocardial infarction is present may require some additional definition of terms. From a clinical point of view, death of a small number of cells that might not be recognizable even if the heart could be examined thoroughly at autopsy, without associated malignant dysrhythmia or impaired ventricular performance, may have implications no different from those of a severe episode of coronary insufficiency without necrosis. In the first case, transitory, modest elevations of plasma MB CK might be detectable, but in the absence of all other criteria of infarction the result might be considered inappropriately as "false positive." The question of whether or not infarction is present may not be the same question as whether or not the clinical syndrome associated with a diagnosis of myocardial infarction is present.

On the other hand, it is obvious that release of enzymes and other intracellular constituents can occur under experimental circumstances in which ischemia is absent. Perfusion of myocardium with calcium-free medium leads to liberation of enzymes without cell death.[8] Nevertheless, in experi-

mental studies in which coronary occlusion has been maintained for selected intervals before protracted sampling of peripheral blood for enzymes released from the heart, the presence of necrosis and elevated plasma MB CK activity were concordant.[9] In keeping with results from a large number of clinical studies, these and other experimental findings suggest that when plasma enzyme elevation results from myocardial ischemia, the ischemia has been sufficient to produce irreversible injury to the heart.[10]

When one seeks to examine the frequency of false negative results of the diagnosis of myocardial infarction based on analysis of MB CK in plasma, sampling frequency becomes an important consideration. The standard deviation of results of MB assay by radioimmunoassay in samples obtained repetitively from the same patient is remarkably small, and the normal range for MB activity quite narrow. Accordingly, even modest elevations of MB CK are detectable with this technique.[11] However, when the amount of myocardial cell death is modest, elevations may be transitory since clearance of MB CK from the circulation may be nearly as rapid as MB release from the heart and since the total amount of enzyme liberated into the circulation may be small. For these reasons, failure to obtain samples frequently enough may lead to a lack of detection of infarction and results may be inappropriately characterized as "false negatives."

The presence or absence of MB CK in tissues besides the heart has received considerable attention. Clearly, exclusive distribution of MB CK in myocardium would offer potential advantages and facilitate interpretation of elevated MB in plasma. However, it is well recognized that isoenzyme profiles differ in normal compared with dystrophic skeletal muscle, and that the profiles in developing compared with mature tissue are not necessarily the same. Furthermore, in embryonic tissue from most organs, B subunits of CK are prominent even if the adult organ is destined to exhibit only the MM isoenzyme. Accordingly, it is unrealistic to expect that MB CK will be absent from all organs besides the heart under all conditions. To determine whether substantial amounts of MB CK are present in skeletal muscle from adult subjects, extracts have been studied with qualitative assays by several groups.[6,7,12-16] The trace or modest amounts detected by some may have been due to several factors besides the presence of MB CK itself such as nonspecific fluorescence from moieties other than reaction products of the CK enzyme, reaction products generated by enzymes such as myokinase rather than CK, inclusion of isoenzymes besides MB in the region of the chromatogram or electrophoretogram in which MB was anticipated due to unavoidable overlapping of peaks or overloading medium when the relative contributions from different isoenzymes were markedly disparate. Although quantitative assays have indicated trace amounts of MB in tissues such as prostate and mucosa of the gastrointestinal tract, appreciable quantities of MB CK have not been detectable consistently in extracts of skeletal muscle.

From the clinical point of view, the important issue may be approached pragmatically—namely by assessing the extent to which trauma to skeletal muscle leads to elevations of MB activity in plasma that could conceivably result in false positive diagnoses of myocardial infarction. Among patients subjected to intramuscular injections, noncardiac surgical procedures involving the head and neck, ocular muscles, the thorax, abdomen or extremities, and those experiencing soft tissue injury in association with procedures such as cardiac catheterization, plasma MB CK is not elevated despite pronounced elevations in total plasma CK activity and assessment of samples over relatively long intervals following the trauma to skeletal muscle.[3,17,18] A similar dichotomy was observed in cases of rhabdomyolysis with several thousandfold elevations of total CK but persistently normal MB CK (unpublished observations). Therefore, it seems unlikely that elevations of MB CK due to release of enzyme from skeletal muscle will obscure the diagnosis of myocardial infarction based on plasma MB CK as a criterion, and accordingly, analysis of plasma MB activity is useful in detection of infarction even among patients undergoing noncardiac surgical procedures.

Analysis of plasma enzyme time-activity curves has been employed to estimate the extent of infarction as well as to detect it in the clinical setting.[19-21] Although myocardial CK depletion, measured directly, generally correlates with CK recoverable in blood after infarction in experimental animals, poor correlations will result if right ventricular infarction is not taken into account. In addition, in most experimental animal species, MB CK is present in numerous tissues besides the heart and the proportion of MB in myocardium is much less than that in myocardium in man. Accordingly, use of animals subjected to

surgical operation or anesthesia during the interval in which the infarct is assessed, or difficulties related to quantitative assessment of small amounts of MB on backgrounds of very large amounts of total plasma CK may lead to erroneous estimates of infarct size based on analysis of serial changes in plasma MB activity. Recent results in experimental animals are consistent with the view that even pronounced hemodynamic perturbations or exposures to drugs utilized in the clinical setting fail to alter enzymatic estimates of infarct size substantially.[21,22] Improved characterization of processes governing release of enzyme from the heart and its clearance from the circulation have led to refinements in models utilized to estimate the extent of infarction based on analysis of plasma time-activity curves. Since it is now clear that CK, like many other proteins, is distributed in at least one extravascular compartment and that the observed elimination rate underestimates the true disappearance rate because of resupply of the vascular from the extravascular pool, more of the enzyme lost from the heart undergoing ischemic injury can be accounted for than was possible with simpler models.[23] Therefore, although relative estimates of infarct size previously reported would not be affected, the increased proportion of enzyme accounted for with two-compartment models suggests that percentage errors introduced by variations in the ratio of enzyme lost from the heart compared with that released may be considerably smaller than had been thought previously.

From the clinical point of view, it is of interest that infarct size estimated from analysis of plasma MB and total CK time-activity curves has correlated with several sequelae of infarction as reported by many investigators and recently reviewed.[24] These sequelae include the frequency of ventricular premature beats during the first ten hours after hospital admission, the impairment of left ventricular performance assessed both by radionuclide angiocardiography in patients studied 24 to 48 hours after admission and in those studied even earlier by left ventricular angiocardiography, hemodynamic decompensation, the mass of left ventricle exhibiting dyskinesis, pulmonary vascular congestion, impaired ventricular compliance, recovery of exercise tolerance in the convalescent period, morphologic estimates of infarction based on histochemical analysis of the heart at postmortem, and early mortality. Analysis of plasma enzyme time-activity curves, therefore, provides prognostic as well as diagnostic information.

As Dr. Guzy points out, "CPK-MB appears to be the most sensitive and the most specific indicator of an acute MI available." Interest in quantitative considerations related to this particular biochemical marker has led to some clarification of the behavior of intracellular constituents from myocardium undergoing irreversible injury in general. Initially empirical models have been improved by incorporation of mathematical representations of physiological processes influencing release of such markers from the heart and their clearance from the circulation. Continued development and experimental verification of such models should permit the continued refinement of enzymatic estimation of the extent of infarction as well as the rapidity and specificity of its diagnosis.

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Of Medical Problems and Social Problems

THE RELATIONSHIPS between medicine and society have often been discussed in these columns. It has frequently been suggested that medicine has something to offer toward the resolution of many social problems when these affect health and health care, and that society needs genuine and constructive help from the medical profession if it is to deal successfully with the social and economic problems of access to and delivery of patient care. These interactions between medicine and society have occurred all too seldom. Rather the pattern seems to have been for each to square off in opposition to the other and this really has got no one anywhere. Perhaps it is time to examine some other approaches. For example, can anything be learned from the prototype model of patient care—the interactions which take place in the doctor-patient relationship—or from the way a physician deals with a complex medical problem within this relationship? After all the essential ingredients—medicine, society, health and health care—are basically the same although the dimensions are different.

If one examines what a physician does and what a patient does in the doctor-patient relationship and the approach to a complex medical problem, one indeed can see many parallels with what might be a relationship between the medical profession and society and its government, in a new kind of approach to broader social problems which affect health and health care. First it is necessary for both doctor and patient (or for medicine and society) to agree that there is a problem. Having recognized that a problem exists, an attempt is made to describe and define the problem as objectively as possible. The present illness, as described by the patient, gives some assessment of its nature and extent. The past history and social history may explain how things got to where they are and identify factors which may be important in diagnosis and treatment. The problem is then examined physically where it is, again as objectively as possible. Next measurements are made through laboratory and other kinds of studies. As accurate a data base as possible is established. Then consultations may be held and professional knowledge and experience are brought to bear to develop the diagnostic possibilities or probabilities and possible courses of action. These are then discussed with the patient, the patient's family and whoever else may be involved in carrying out the treatment process. All must be convinced that this is what should be done. Then there must be agreement among all concerned as to who is to do what in carrying out the treatment. Then and only then can a successful action program be undertaken. The later steps are to monitor progress, and to improve and refine the definition of the problem, the data base, the diagnosis and treatment. This approach continues until the problem is solved or an acceptable steady state is reached.

It would seem that there may be something to be learned from this. Would it not be reasonable to try to apply the steps and the approach of the physician-patient model just described to the relationships between medicine and society, between the medical profession and government for instance, in dealing with broad social problems affecting health and health care?

Recent events in California suggest that this may not only be possible but also feasible. The House of Delegates of the California Medical Association, frustrated in its attempts to deal with the medical malpractice crisis by direct confrontation, recognized the medical liability insurance problem to be symptomatic of a much broader social problem involving liability of all kinds and the effects our tort system of law has had upon the field of liability. The House then proceeded to set in motion a series of steps to deal with this complex social problem exactly as a physician would approach a complex problem in patient care. It caused there to be created an independent California Citizens Commission on Tort Reform (CCCTR), which found out all it could about the problem, including the present illness, the past history and the social history, and then examined this information as objectively as possible. A study was authorized to measure the number of poten-

tially compensible events occurring in California hospitals. This was called a Medical Insurance Feasibility Study. An ad hoc Committee on Tort Reform Alternatives was created within the Association to consider possible courses of action.

The next steps are yet to be taken, but will involve recommendations for action which will need to receive agreement of all who must be involved in carrying out the recommendations in both medicine and society, if the treatment is to be accomplished successfully. In this approach the medical profession has found itself in the role of physician to society, which has a problem affecting health and health care. The physician has helped in the diagnosis and treatment. But equally important, the patient, society, has, as it always should, played an equally essential role. The part played by the medical profession in this instance has been both appropriate and acceptable for physicians, and while the process is by no means completed and the outcome is still in the future, it bodes well that at long last medicine is using its professional problem-solving skills to address a major social problem affecting health and health care.

—MSMW

Technetium 99m Stannous Pyrophosphate Myocardial Scintigraphy to Detect Myocardial Necrosis

IT IS CLEAR that there are a number of different clinical circumstances in which traditional techniques that have been used for years are not adequate to conclusively identify or exclude the possibility of recent myocardial infarction. In particular, electrocardiograms (ECG) may not adequately show new myocardial infarcts in leads with "scar patterns" reflecting previous myocardial damage, in patients with left bundle branch block and in those persons in whom cardioversion recently has been done. The subendocardial region is the one most vulnerable to injury during experimental myocardial ischemia, but subendocardial ischemia cannot be precisely distinguished on ECG's from subendocardial infarction. Further, the ST and T wave changes of subendocardial injury resulting from coronary artery disease cannot be absolutely differentiated from those occurring with rapid heart rates, electrolyte alterations, left ventricular hypertrophy with strain and certain medications including—it is important to note—cardiac glycosides.

The usefulness of measuring cardiac enzymes in detecting acute myocardial necrosis, particularly the "myocardial specific" isoenzyme of creatine kinase (MB or B subunit),[1-3] is recognized but there are also certain limitations in this approach. Included among these limitations are temporal restrictions (for example, serum enzyme testing must be done within 18 to 20 hours of the onset of symptoms suggesting infarction or else the creatine kinase-MB isoenzyme value may be normal independent of the presence or absence of infarction). The MB isoenzyme of creatine kinase is often increased in sera of patients undergoing open heart surgical procedures even in the absence of perioperative myocardial infarction and, therefore, this represents another clinical situation in which precise identification of the presence or absence of infarction may be difficult.

There are then definite diagnostic limitations in the usefulness of traditional determinants for infarct recognition and consequently there is a need for more sensitive and specific noninvasive diagnostic tests. There are also additional reasons indicating the necessity to develop new noninvasive means for infarct detection and these include the desire to be able to localize and size the extent of myocardial damage occurring with infarction. Concern about infarct localization and size stems from the fact that such knowledge should help one to predict subsequent clinical course, such as heart block, cardiogenic shock, medically refractory congestive heart failure or the development of medically refractory ventricular arrhythmias.[4-6]

For these reasons, approximately three years ago a noninvasive myocardial imaging technique utilizing technetium 99m stannous pyrophosphate (^{99m}TcPYP) was developed at The University of Texas Southwestern Medical School in Dallas.[7-10] To date, this myocardial imaging test has been utilized for diagnostic purposes of infarct detection in approximately 4,000 persons admitted at our institution with chest pain.

Our general findings with this myocardial imaging technique for infarct detection are similar to those reported by Werner and his colleagues in this issue of the WESTERN JOURNAL. Specifically, we have found the technique to be useful in identifying acute transmural and nontransmural

infarction in a variety of different clinical circumstances,[8-10] in identifying myocardial necrosis resulting from causes other than coronary artery disease,[11-12] in sizing acute anterior and anterolateral infarcts in experimental animals and in man[13-15] and in excluding the presence of myocardial infarcts that are larger than 3 grams in size. We feel that the deposition of calcium in crystalline and precrystalline form in severely damaged myocardial cells generally accounts for the development of a positive ^{99m}TcPYP myocardial scintigram[16] although there may also be another mechanism, or other mechanisms, that are also involved in incorporation of ^{99m}TcPYP into dead and dying myocardial cells.[17] Calcium deposition in the heart, such as occurs in patients with severe renal insufficiency and elevated serum calcium-phosphorus products, can also result in an abnormal ^{99m}TcPYP myocardial scintigram. This suggests that calcium deposits (in some form) might generally result in abnormal ^{99m}TcPYP myocardial scintigrams. This might explain the abnormal scintigrams noted in some patients with heavily calcified and large ventricular aneurysms and in some with heavily calcified cardiac valves. It should also be remembered, however, that calcium deposition per se may be associated with the subsequent development of myocardial fibrosis and necrosis and that a positive ^{99m}TcPYP scintigram in some circumstances may be a secondary consequence of calcium deposition.

Accurate infarct sizing of acute inferior, true posterior or nontransmural (subendocardial) infarcts is not yet possible using pyrophosphate scintigraphy. This is due to the fact that currently available imaging cameras and the projections that are utilized provide only a two-dimensional or area estimate of the size of the lesion. ^{99m}TcPYP scintigraphy is capable of sizing acute anterior or anterolateral infarcts since the overall extent of the myocardial damage can be visualized, but it is inadequate for sizing other types of infarcts because the absolute extent of the lesion is not identified. Presumably, the development of tomographic cameras that can be used with nonpositron emitting radionuclides or computer assisted techniques for three-dimensional infarct reconstruction[14] will allow one to use ^{99m}TcPYP scintigraphy to size other types of infarcts, but this is a matter that will have to be rigorously tested in the future.

One other matter deserves consideration in any discussion of the efficacy of a new diagnostic test: What is the "gold standard"' against which this test is to be judged? In clinical medicine the gold standards are often less than exact. This inevitably leads to somewhat different impressions regarding the sensitivity and specificity of a particular test. Apart from a detailed morphological assessment there is no totally acceptable gold standard for infarct recognition and, therefore, one is limited to comparisons and correlations with techniques that are themselves less than perfect in identifying myocardial necrosis to establish the accuracy of ^{99m}TcPYP myocardial scintigraphy. I can offer no ready solution to this dilemma except to suggest that ultimately careful morphological comparisons with the results of ^{99m}TcPYP scintigraphy in patients and appropriate experimental animal models should help to establish the specificity and sensitivity of this imaging technique in the recognition of myocardial necrosis. Such correlations should allow one to determine why in a third of patients with unstable angina pectoris positive ^{99m}TcPYP myocardial scintigrams develop[10] and why some patients have persistently positive myocardial scintigrams after infarction.[18] From several previous studies it should be expected that acute myocardial necrosis, whatever its cause, amounting to 3 grams or more in extent and with some persistent coronary blood flow to the area of damage will be associated with an abnormal ^{99m}TcPYP myocardial scintigram.[11-14,16,18]

There is one point in the clinical experience of Werner and associates utilizing ^{99m}TcPYP myocardial scintigraphy that surprises me: the relative inability of the technique to detect acute subendocardial myocardial infarcts in these investigators' experience. Werner, Botvinick and co-workers believe that the "poorly localized (diffuse) 2 plus" positive ^{99m}TcPYP scintigrams are less specific for infarct detection than the more positive better localized patterns ("3-4 plus") of increased ^{99m}TcPYP uptake. Originally, this might have accounted for the relatively poor "batting average" in subendocardial infarct detection since in our experience approximately two thirds of patients with this type of lesion have "2+ poorly localized" patterns of ^{99m}TcPYP myocardial uptake. Werner, Botvinick, Shames and Parmley are correct, however, that the "2+" pattern of ^{99m}TcPYP uptake is the "trouble area" for this imaging test since red blood cell labeling with free ^{99m}Tc-pertechnetate and a persistently positive radionuclide blood pool scintigram, delayed clearance of the radionuclide blood pool scintigram

either because of severe ventricular dysfunction or renal insufficiency may also result in what might mistakenly be interpreted as a "2+ diffuse" ^{99m}TcPYP myocardial scintigram.

This imaging test, therefore, must be utilized with careful attention to technical detail and with imaging cameras of high resolution and good image quality in order to detect infarcts (or myocardial necrosis whatever the cause) with sensitivity and specificity. There is no a priori reason for acute nontransmural (subendocardial) infarcts to be significantly more difficult to detect than similar sized transmural ones; some might even be easier, but this probably depends on the extent of the coronary artery disease associated with the infarct. We have noticed that serial myocardial imaging with ^{99m}TcPYP (at least two scintigrams between 24 and 120 hours after the onset of symptoms suggestive of infarction) allows one to detect some patients with myocardial infarcts that would have otherwise been missed. Perhaps, failure to obtain serial ^{99m}TcPYP myocardial scintigrams is the most likely explanation for missing a relatively large percentage of acute subendocardial infarcts in patients. In our experience, serial myocardial imaging is particularly likely to be necessary in patients with severe and extensive intrinsic coronary artery disease. This is probably due to the fact that the development of enough collateral coronary blood flow to allow the damaged area to be visualized with ^{99m}TcPYP scintigraphy may require a little longer when extensive intrinsic coronary disease exists. We feel that serial myocardial imaging with this technique is terribly important for the reasons mentioned above and also to help distinguish old from new damage in those patients in whom the scintigrams are persistently positive.[18]

^{99m}TcPYP myocardial scintigraphy is not a perfect test, but as Werner and co-workers point out it does appear to be a useful addition to our armamentarium for the noninvasive recognition of acute myocardial infarcts. This imaging technique may also become clinically useful in sizing infarcts if three-dimensional reconstruction of the infarct image is made possible by further equipment developments in the future.

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CASE REPORTS

Refer to: Sacks DA, Niswander KR, Easton TH: Tubo-ovarian abscess at puberty. West J Med 127:513-514, Dec 1977

Tubo-ovarian Abscess at Puberty

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TUBO-OVARIAN ABSCESS is a known complication of pelvic inflammatory disease. It is most commonly found in sexually active women during the reproductive years. It has been infrequently reported in postmenopausal women.[1-3] The occurrence of a tubo-ovarian abscess in a sexually inactive girl at puberty is extremely unusual. To share our problems regarding the cause, diagnosis and management of this entity, we submit this report.

Report of a Case

The patient is a 12-year-old girl who one year before admission had her first and only menstrual period. She was asymptomatic until five days before admission, when she noted the insidious onset of right lower quadrant pain. The pain was dull in quality, constant and nonradiating. Over the four days before admission the patient had been anorectic and nauseated, and had had several episodes of vomiting. Enemas administered by her mother caused a transient increase in the intensity of her pain. She had been subjectively febrile without chills for the two days before admission. She said that there had been no hematemesis, hematochezia, melena, backache, flank pain or dysuria. She said she had never had sexual intercourse. She did give a history of a chronic yellow vaginal discharge with no itching or burning. The only surgical operation in the history was an appendectomy carried out two years before admission.

On physical examination, the patient was a well-developed girl in moderate acute distress. Her temperature on admission was 39.11°C (102.4°F). On abdominal examination there was tenderness and rebound in all quadrants, maximal in the right lower quadrant. On pelvic examination there was a scant amount of pubic hair. The hymenal ring appeared intact. There was a scant amount of yellow vaginal discharge. Vaginal and rectal examinations, carried out with difficulty because of the patient's tenderness and guarding, showed a cystic, tender, 4 cm in diameter right adnexal mass which appeared to be fixed in the cul-de-sac, posterior to the uterus.

Admission laboratory data included a hemoglobin value of 14.3 grams per 100 ml and leukocyte count of 13,000 with 52 segmented and 34 nonsegmented neutrophils. Cervical Gram stain showed 3+ leukocytes and 4+ Gram-positive bacilli.

With a presumptive diagnosis of torsion of the right adnexa, the patient was taken to the operating room. Examination under anesthesia confirmed the previous pelvic findings. Laparotomy showed a right tubo-ovarian abscess. The right adnexa was adherent to the sigmoid colon. In the process of mobilizing the right adnexa the abscess was inadvertently ruptured. Its contents consisted of yellowish, purulent, foul-smelling liquid. The left tube and ovary were grossly normal. The abdominal viscera were palpated and felt to be normal. In view of the patient's youth, and the normal appearance of the left adnexa, only the right tube and ovary were excised. At the close of the procedure the peritoneal cavity was drained via two Penrose drains tied to a Malecot catheter passed through the cul-de-sac to the vagina. Before the closure of the peritoneum, the abdominal cavity was irrigated with penicillin solution.

Postoperatively the patient was empirically begun on a regimen of 30 million units of aqueous penicillin given intravenously and a gram of kanamycin given intramuscularly in divided doses each day. Her temperature peaked at 39.89°C (103.8°F) four hours postoperatively. By the second postoperative day she became afebrile. The

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vaginal drains were removed on the fifth postoperative day. She was discharged on the seventh postoperative day.

Cervical cultures grew mixed flora. Cultures from the abscess cavity grew peptococcus, bacteroides melaninogenicus and fusobacterium species.

Discussion

Tubo-ovarian abscess is usually a sequella of recurrent pelvic inflammatory disease.[4] It is most commonly found during the third and fourth decades of life. Rarely is it seen in preadolescents. Mickal and Sellmann[5] reported that only five of 741 patients with tubo-ovarian abscesses were within the 10- to 19-year-old age group. Only 3 percent of 143 patients with ruptured tubo-ovarian abscesses in Pedowitz and Bloomfield's series were below the age of 20.[2]

The absence of historical and physical findings suggesting primary pelvic inflammatory disease in our patient prompts speculation regarding the cause of the abscess. The primary event could have been torsion of the adnexa, followed by necrosis and infection. Bahary and Eckerling,[6] reporting on torsion of previously normal fallopian tubes and ovaries, noted an increased mobility of these organs, particularly in adolescents.

That the ascending route may not be the only means of adnexal abscess formation is suggested by some reports of pelvic infection in pregnancy. Acute salpingitis[7] as well as ovarian and tubo-ovarian abscesses[8-10] have been reported during all trimesters of pregnancy. Friedman and Bobrow[9] postulate that in pregnancy pathogens may be carried to the adnexae by either the hematogenous or lymphatic routes. They, as well as Buckle,[11] suggest that a preexisting ovarian cyst may be a site for abscess formation.

It is interesting to speculate on the possible relationship between our patient's previous appendectomy and the subsequent tubo-ovarian abscess. Skirrow and Prakash[12] reported a nulligravida who, 38 years after appendectomy, was found to have a right tubo-ovarian abscess with grossly normal left adnexa. Greenwald and Fenton[13] reported a patient who three months following incidental appendectomy at cesarean section developed a right ovarian abscess. Ledger and associates[14] reported the cases of 19 patients, in the reproductive age group, in whom adnexal abscesses developed from 6 to 133 days following pelvic surgery. There appears, therefore, to be evidence that previous appendectomy or pelvic surgical operation (or both) predisposes to delayed development of adnexal abscess. Perhaps, as Ledger suggests,[14] the ovulation site serves as a nidus for bacterial invasion of the ovary.

While our selection of operation was based more on empiricism than experience, controversy exists regarding the management of both ruptured and unruptured tubo-ovarian abscesses. Willson and Black[15] limited surgical operation to removal of the affected ovary in over half their patients with unruptured ovarian abscesses. Walker and Baker[16] stressed that surgical procedures be as complete as possible in cases of pelvic infection refractory to medical management. On the basis of their experience with unruptured tubo-ovarian abscess, Nebel and Lucas[17] felt that anything less than total extirpation of the pelvic viscera is of little merit. Pedowitz and Bloomfield[2] recommended removal of the uterus, tubes and ovaries, in the presence of a ruptured tubo-ovarian abscess. On the other hand, Mickal and Sellman[5] and Collins and Jansen[18] suggested limiting surgical removal to the diseased organs only. Our experience suggests that when the contralateral tube and ovary do not appear infected, it may be reasonable to remove only the abscessed adnexa, drain the pelvis and administer high doses of antibiotics.

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Refer to: Fuller CM, Yassinger S, Donlon P, et al: Haloperidol-induced liver disease. West J Med 127:515-518, Dec 1977

Haloperidol-Induced Liver Disease

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HALOPERIDOL, a widely used neuroleptic, is a butyrophenone drug with phenothiazine-like properties useful in the management of psychosis. Adverse reactions attributed to haloperidol include effects on the extrapyramidal system including parkinsonian symptoms and tardive dyskinesia, agranulocytosis and limb malformations in the fetus when the drug is taken during the first trimester of pregnancy.[1] Liver dysfunction has previously been reported only as a rare complication of haloperidol therapy. Since 1967 we are unaware of any published reports of haloperidol hepatotoxicity. In this report, two cases are described in which significant hepatic dysfunction developed while patients were being treated with haloperidol.

Methods

Routine laboratory tests were done in Sacramento Medical Center-University of California, Davis, clinical laboratory. Serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) values were determined by the methods of Henry[2] (normal ranges for SGOT and SGPT are 0 to 20 units per liter and 0 to 15 units per liter, respectively). Serum alkaline phosphatase was determined by the method of McComb and Bowers (normal range 20 to 80 units per liter).[3] Serum bilirubin was determined by the Jendrassick-Grof method.[4] Hepatitis B surface antigen was determined by radioimmunoassay (Ausria II-125 kits, Abbott Laboratories, North Chicago, Illinois).

Material from the percutaneous liver biopsy specimens was fixed in 10 percent formalin and routinely processed for light microscopy. Sections were stained with hematoxylin and eosin,[5] Goldner-Foot's modification of Masson's trichrome stain,[6] Lillie's reticulum stain[7] and Mallory's stain for iron.[5]

Reports of Cases

PATIENT 1. A 33-year-old chronically schizophrenic woman was followed for five years as an outpatient before admission. During that time she received various neuroleptic agents including haloperidol, fluphenazine and benztropine mesylate. Three months before the patient's admission, overt psychotic behavior developed and she was treated with fluphenazine and benztropine mesylate, with resolution of psychotic symptoms. Two weeks later a generalized erythematous rash developed at which time administration of fluphenazine and benztropine mesylate was discontinued and therapy with thiothixene was started. Psychotic decompensation again recurred, and haloperidol was substituted for thiothixene. For the first two weeks of haloperidol therapy, benztropine mesylate was administered for control of extrapyramidal symptoms, and then this treatment was discontinued. Maintenance haloperidol usage was 40 mg per day. Results of liver function tests were normal at the start of haloperidol therapy. Five weeks after initiation of treatment with haloperidol, the patient complained of anorexia, nausea, vomiting, lethargy, fever and lower extremity rash. The following test values were obtained: total bilirubin, 4.2 mg per 100 ml; SGOT 100 IU per liter; and SGPT, 130 IU per liter. Haloperidol therapy was discontinued. Because symptoms persisted, the patient was admitted to hospital five days later. She said there was no previous history of similar symptoms, jaundice, recent surgical operation or general anesthesia, other medications, ethanol use or illicit intravenous drug use. The patient had discontinued the use of oral contraceptives three months before the onset of her illness. She had been in contact six months previously with a person said to have had hepatitis.

On physical examination, the patient appeared to be in a toxic condition though nonicteric. Temperature was 38°C (100.4°F); blood pressure supine was 120/80 mm of mercury, and sitting

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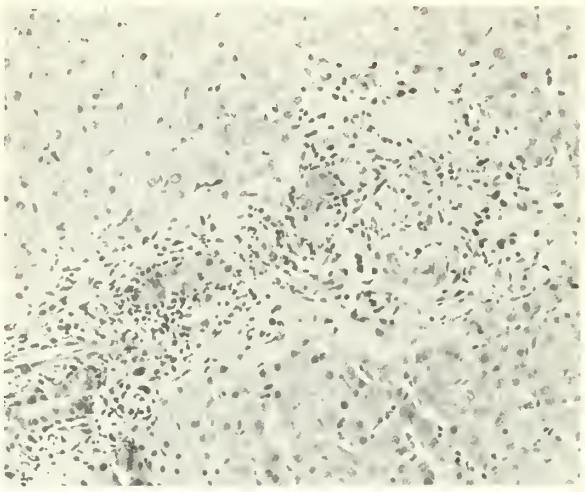

Figure 1.—(Case 1) Note edema and massive infiltration of inflammatory cells, predominantly eosinophils, in the vicinity of portal bile ducts. Hematoxylin and eosin stain, reduced from ×400.

it was 80/40 mm of mercury; pulse supine was 100, sitting 120; and respirations 14. There was a general red erythematous macular rash over the lower extremities and palms. On examination of the abdomen, mild right upper quadrant tenderness was noted, but no liver or splenic enlargement. The remainder of the examination gave unremarkable findings.

Laboratory studies gave the following values: hematocrit, 39.3 percent; leukocyte count, 12,800 with 29 percent polymorphonuclear neutrophils, 20 percent band forms, 48 percent lymphocytes and 3 percent eosinophils; platelet count and prothrombin time, normal; serum sodium, 136 mEq per liter; potassium, 3.2 mEq per liter; bicarbonate, 31 mEq per liter; chloride, 96 mEq per liter; blood urea nitrogen, 9 mg per 100 ml; glucose, 120 mg per 100 ml; total bilirubin, 2.5 mg per 100 ml; conjugated fraction, 1.5 mg per 100 ml; SGPT, 100 IU per liter; alkaline phosphatase, 486 IU per liter, and hepatitis B surface antigen, negative.

Intravenous replacement of volume deficit was given and the patient's condition improved. A liver biopsy was done on the second hospital day and the specimen showed a normal general architecture. There was pronounced edema of the portal triads with a heavy infiltrate of esosinophils, polymorphonuclear leukocytes and occasional mononuclear cells (Figure 1). A few small areas of necrosis were noted throughout the parenchyma. The pathological impression was that the changes represented a hypersensitivity reaction, predominantly cholestatic, but also hepatocellular. The patient was discharged and followed in the outpatient clinic on a regimen of loxapine. All symptoms resolved and liver function tests returned to normal. Subsequent double-dose cholecystography failed to visualize the gallbladder, but intravenous cholangiography showed a normal biliary ductal system.

PATIENT 2. A 27-year-old woman was referred to UC Davis-Sacramento Medical Center because of jaundice. She had been entirely well until January 1976, when she was admitted to hospital with an acute paranoid schizophrenic reaction. She was treated with haloperidol in doses up to 20 to 25 mg per day and her condition improved. After 11 days of haloperidol therapy, she discontinued taking the medication because of dry mouth and blurred vision. Psychotic symptoms recurred and haloperidol was reinstituted along with benztropine mesylate. Four weeks after the initial dose of haloperidol, painless jaundice, dark-colored urine and acholic stools were noted. She said she was taking no other medications and that there was no history of alcohol or drug abuse, previous jaundice, hepatitis, gallbladder disease or abdominal surgical procedures. She was admitted to a local hospital and haloperidol therapy was discontinued. Total bilirubin was found to be 10.4 mg per 100 ml and serum alkaline phosphatase was 360 units per liter; results of other chemical studies, including SGOT and serum cholesterol determinations, were within normal limits. Ultrasound examination showed no evidence of gallbladder enlargement or dilatation of the biliary tree. She was then transferred to UC Davis-Sacramento Medical Center for further evaluation.

On physical examination the patient was afebrile and icteric. There were no stigmata of chronic liver disease. The heart and lungs were normal. The liver was 9 cm in length and the edge was nontender. The spleen was not palpable. There was no peripheral edema. The remainder of the physical examination showed no abnormalities.

Laboratory studies, including a normal complete blood count and differential, gave the following values: SGOT, 85 IU per liter; total bilirubin, 15.8 mg per 100 ml; conjugated fraction, 8.1 mg per 100 ml; alkaline phosphatase, 310 IU per liter; serum cholesterol, 300 mg per liter; serum albumin, 4.2 grams per 100 ml; hepatitis B surface antigen, negative.

In order to rule out extrahepatic biliary obstruction, endoscopic retrograde cholangiopancreatog-

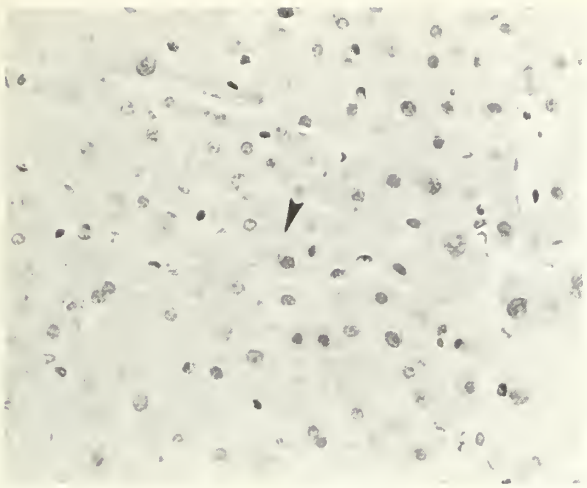

Figure 2.—(Case 2) Note bile plugs **(arrow)** in canaliculi. Mallory's stain for iron, reduced from ×1,000.

raphy was carried out. A normal biliary tree was visualized. Percutaneous liver biopsy showed a normal overall architecture. The portal triads showed a scanty inflammatory infiltrate composed of round cells. There were moderate numbers of bile plugs in canaliculi (Figure 2), predominantly in central zones. There was no hepatocellular necrosis, granulomas or neoplasia. A diagnosis of drug-induced intrahepatic cholestasis was made. The patient was discharged to the care of her private physician and within four weeks, the jaundice abated.

Discussion

Before 1967 there were 21 reported cases of liver dysfunction associated with haloperidol therapy. Jaundice was not observed in all of the cases, and in none was a liver biopsy performed. In 1966, Gerle critically reviewed the first 18 cases from a patient population of 12,600 and suggested that haloperidol therapy could only be implicated in two of them.[8] Crane added three more cases in 1967, and concluded that the incidence of this disorder was approximately two per one thousand cases.[9] Ebert felt these incidence figures were similar to those for viral hepatitis, and therefore a distinction could not be made.[10] In 1972 Ayd suggested that the development of jaundice in a patient receiving haloperidol was not a contraindication to retreatment with the drug.[11]

Our two cases of presumed haloperidol-induced liver dysfunction with jaundice appear to be the first reported with liver biopsy confirmation. The finding of edema and a heavy infiltrate of eosinophils in the portal triads of the liver biopsy in case 1 is consistent with hypersensitivity-induced cholestasis. In this patient, the development of a rash, fever, leukocytosis and eosinophilia are consistent with hypersensitivity. The elevation of alkaline phosphatase with mild hyperbilirubinemia is in keeping with a predominantly cholestatic reaction. The slight focal hepatic necrosis and the mild elevations of SGOT and SGPT levels indicate mild hepatocellular damage. The close temporal relation between haloperidol therapy and the appearance of hepatic dysfunction as well as the absence of reported cases of drug-induced liver injury with fluphenazine, benztropine or thiothixene suggest that haloperidol may have been responsible for this hypersensitivity reaction.

Case 2 presented classic symptoms and signs of cholestatic jaundice. Extrahepatic biliary obstruction was ruled out by a normal biliary tree at endoscopic retrograde cholangiopancreatography. Other drugs which can cause cholestatic features, such as analgesics, antiarthritics, antibiotics, sedatives, anticonvulsants, thyroid medications, antihypertensives, diuretics and hormonal agents had not been administered. The development of jaundice shortly after initiation of haloperidol therapy and its resolution soon after its discontinuance suggests a cause-and-effect relation between haloperidol and the cholestasis.

These two cases represent the two histologic types of hepatic lesions seen in hypersensitivity cholestasis.[12] Our first case also showed some hepatocellular damage. These two cases, therefore, show both cholestatic and hepatitic sensitization reactions. It is well established that some drugs may cause either response on different occasions,[13] as is reported here. Other drugs that can cause either a hepatic or cholestatic hepatitis include indomethacin, phenylbutazone, novabiocin, propylthiouracil and diphenylhydantoin.

While haloperidol is felt to be responsible for the significant hepatic dysfunction in the above two cases, it is possible that benztropine mesylate was the offending drug because both patients received benztropine mesylate along with haloperidol before the onset of their hepatic dysfunction. This seems unlikely because benztropine mesylate is a combination of the active portions of atropine and diphenhydramine;[14] neither the parent compound nor either of its components has been reported as a cause of liver dysfunction. In contrast, haloperidol has been cited as a rare cause of hepatotoxicity.[8-10] To be more certain, however, would have required readministering both drugs to

the patients. Because this procedure can cause recrudescence of the hepatic injury, it was felt that rechallenge was not ethically justifiable. In spite of not being absolutely certain as to which drug was responsible, we felt that since haloperidol is such a commonly used neuroleptic agent, the occurrence of significant liver dysfunction associated with haloperidol and biopsy documentation should be brought to the attention of the general medical community.

The infrequency of reports of similar cases in the past suggests that haloperidol induced liver disease is a rare adverse effect, consistent with a sensitization reaction. Cases may have occurred, but the association possibly went unrecognized. Therefore, when haloperidol is prescribed, the appearance of constitutional symptoms such as fever, chills, arthralgias or skin rash should suggest the possible development of hepatic dysfunction. The determination of liver function tests in these patients may help to ascertain the true prevalence of haloperidol-induced liver disease.

Summary

The cases of two patients in whom liver dysfunction developed during therapy with haloperidol are described. The dosages used were within the range recommended for severely disturbed psychiatric patients. In one patient a generalized hypersensitivity reaction developed; the other patient presented with painless jaundice. Biochemically, both patients showed evidence of mild hepatocellular disease and cholestasis. In neither patient was evidence of extrahepatic biliary obstruction found. Liver biopsy in the first patient showed evidence of a hypersensitivity reaction, with some hepatocellular necrosis, but predominant cholestasis. In the second patient, only cholestasis was seen. Haloperidol is felt to be etiologically related to the liver disease seen in these two patients.

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Refer to: Wheeler M: Gamma benzene hexachloride (KWELL) poisoning in a child—A case of combined cutaneous and oral administration. West J Med 127:518-521, Dec 1977

Gamma Benzene Hexachloride (KWELL) Poisoning in a Child

A Case of Combined Cutaneous and Oral Administration

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GAMMA BENZENE HEXACHLORIDE (GBH), a chlorinated hydrocarbon pesticide that is commonly used as a 1 percent solution or shampoo (KWELL®) for topical treatment of scabies and pediculosis, is potentially very toxic. The following case illustrates the course of a nonfatal ingestion of GBH, a problem of which all who care for children should be aware.

Report of a Case

A 1-year-old boy weighing 10 kg (22 pounds) was brought to the San Francisco General Hospital emergency room by his mother at 4:30 a.m. Half an hour earlier she had found him in bed, limp, unresponsive and breathing irregularly in a gasping manner. He had been well until two weeks before admission; at that time the child had been seen by a private physician and a diagnosis of scabies had been made. The mother had been given prescriptions for 1 percent gamma benzene hexachloride (KWELL) and diphenhydramine (Benadryl®) with instructions to apply the KWELL

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daily, wash it off after 24 hours, and to give one teaspoon of diphenhydramine to the boy by mouth if there was any itching. The bottles were labelled in English. The mother had applied GBH to the boy's body daily for 14 days before admission.

The family babysitter, a conscientious Spanish-speaking woman, stated that she had applied the GBH topically as per instructions at 4 PM on the afternoon before admission. When the patient became irritable and hyperactive, she gave one teaspoon of GBH by mouth at 6 PM. Within five minutes, the boy vomited and continued to do so sporadically throughout the night.

On physical examination at admission, the boy was noted to be well developed, well nourished and afebrile. Pulse was 136, there were sporadic spontaneous respirations at 16 per minute and blood pressure was 90/60 mm of mercury. Fluctuating tonic-clonic seizure activity of the right arm and leg was present, with a definite distal to proximal Jacksonian progression. His mouth twitched to the left, and his eyes were constantly deviated to the left with rapid nystagmus. The child was unresponsive to deep pain stimuli. The pupils were initially 3 mm in diameter and reactive bilaterally, but within two minutes the left pupil was 8 mm in diameter and unreactive. Intravenous infusion of 2 mg of diazepam (Valium®) terminated the seizure activity and the left pupil returned to normal size. Postictal deep tendon reflexes were 3+ and symmetrical, with negative Babinski signs. There was no evidence of trauma or abuse, no rales on auscultation of the lungs and no other abnormalities found on physical examination. Laboratory findings were within normal limits. A urine toxicology screen for opiates, barbituates, and phenothiazines was negative; however, a qualitative screen of the blood for chlorinated hydrocarbons was positive (quantitative blood levels were not obtained).

On the ward, the boy became increasingly responsive to external stimuli, and six hours after admission was essentially normal. He was started on a regimen of 5 mg per day of phenobarbital given by mouth and discharged. Four weeks later an electroencephalogram showed diffuse 4 cps slowing, but by five weeks after discharge, neurologic and developmental findings were normal.

Discussion

Benzene hexachloride is a member of the family of chlorinated hydrocarbon pesticides, the best known of which is DDT (dichlorodiphenyltrichlorethane). Of the six known isomers, gamma benzene hexachloride is the most potent pesticide.[1] Pure GBH, as used in agriculture, is known as lindane and is available in sprays, powders and pellets for use in vaporizers (the most frequently ingested form). GBH is absorbed through gastrointestinal, respiratory and cutaneous routes. Absorption after a single oral dose is variable but appears to be quite poor, perhaps due to the characteristic immediate vomiting. Less than 0.1 percent of an ingested dose appeared in the blood of a child who ingested lindane pellets.[3] A fatal oral adult dose is approximately 100 mg per kg of body weight.[4] However, one child survived ingestion of 110 mg per kg,[2] whereas another died after ingesting 6 mg per kg.[4]

Acute toxicity in adults has also been reported after inhalation of lindane fumes[1,2] and after extensive cutaneous exposure in farm workers. There has recently been a report of repeated topical application of the 1 percent solution of GBH (KWELL) causing convulsions in a child.[17] Approximately 10 percent of a topically applied dose is absorbed systemically in adults (lipoid solvents increase dermal penetration).[5] The metabolic fate in man is not known, except for the fact that, after intravenous or cutaneous administration, 25 percent of the total dose appears in the urine of adult volunteers.[5]

Regardless of how it is absorbed, central nervous system stimulation is the major toxic manifestation of GBH. Its ability to cause seizures is predictable enough to have been used in experimental models to induce convulsions.[6] GBH is concentrated in the white matter of the brain[7] and may cause convulsions by interference with brain ammonia metabolism.[8] The amount required to induce seizures in humans is small: one oral dose of 45 mg has caused seizures in an adult.[2] During seizure activity in one poisoned child, levels of GBH in plasma were only 86 ppm.[3]

In the case reported here there were many but not all of the reported sequelae of GBH ingestion. The total dose administered by the babysitter was small (100 mg topically, followed by 50 mg orally, or a total dose of 15 mg per kg of body weight). The amount absorbed was certainly much less than this but, since blood levels were not obtained and one cannot extrapolate from adult cutaneous absorption to children, the acute systemic dose is unknown. Also, the 14 daily topical applications in our patient had undoubtedly established plasma levels of GBH before the in-

gestion. These previous topical applications may explain why the ingestion of such a small dose caused convulsions.

Vomiting is usually immediate after ingestion, followed by nonspecific signs of nervous system stimulation, such as irritability or hyperexcitability.[1,3,4,8,9] Tonic-clonic convulsions, which usually begin within one to two hours, may last for days.[10] Fixed and dilated pupils, although not unilateral as in our case, have been reported.[9] Hyperglycemia and hyperpyrexia also have been noted,[4,9] as has pulmonary edema in severe cases, and death secondary to respiratory depression.[1] Postmortem, there are signs of liver damage and degenerative changes in the renal tubules.[1,2]

Treatment of a convulsing patient who may have ingested GBH should begin with intravenous administration of phenobarbital (5 mg per kg of body weight) or diazepam (0.1 to 0.3 mg per kg). Diazepam has a theoretical advantage, in that it increases the LD_{50} (lethal dose for 50 percent of survival group) five-fold in mice poisoned with orally given GBH.[11] In all cases of suspected GBH poisoning, ipecac or gastric lavage should be carried out, followed by saline cathartics (oil cathartics should be avoided, as they increase intestinal absorption). The skin should be washed with soap and water if GBH has been applied topically. Administration of epinephrine should be avoided because it might produce ventricular fibrillation.[1]

Few data are available for prognostication.[12] Chronic GBH intoxication has caused mental retardation in children.[12] One child suffered optic atrophy and quadriplegia following ingestion of 30 to 120 mg per kg of body weight.[9] Transient paresis, paralysis and pathologic reflexes also have been described.[13] Clinically, our patient was neurologically and developmentally normal five weeks after ingestion. The abnormal electroencephalographic findings were consistent with previous reports[10,12] of predominance of bilaterally synchronous 4 to 7 cps activity in recovering patients; the electroencephalogram returns to normal in weeks.[10]

Physicians who care for children should appreciate that the margin of safety of 1 percent solution of GBH is not large. High doses should be avoided since the extent of cutaneous absorption of the drug in small children is unknown. Since a single dose is eliminated from adult humans in approximately five days,[5] cumulative toxicity could result from repeated topical applications during this time. The Food and Drug Administration has pointed out that recent publications have recommended application of KWELL lotion as often as four times in three days.[14] The manufacturer suggests one application to the entire body is to be left on for 24 hours with a repeat treatment in four to seven days, if necessary.[15] Since children have a higher surface area to body weight ratio than adults, and because cutaneous absorption data are not available for the pediatric age group, others[16] recommend the use of scabicidal agents with a greater margin of safety in infants and children. Another effective scabicidal agent, crotamiton (Eurax®), is available commercially. Solutions of 6 percent precipitated sulfur or 20 percent benzyl benzoate are agents that are used principally by dermatologists and must be compounded by a pharmacist. The use of these agents is well described by Orkin and associates.[16] If one percent solution of GBH *is* prescribed, the following precautions should be taken:

- Calculate and dispense the exact amount needed without refill (approximately 30 ml of solution will completely coat the surface of an adult).
- Avoid repeated use within one week.
- Label the bottle clearly, with directions for use and poison warnings in the language of the patient and immediate family or caretakers.
- Do not dispense 1 percent solution of GBH with other medications it could be confused with.

In general, 1 percent GBH (KWELL) should be included in any list of drugs which when ingested can cause seizures in children.

Summary

A 1 percent solution of gamma benzene hexachloride (KWELL) is a commonly used scabicide that is potentially very toxic. A case is reported of nonfatal oral poisoning in a child illustrating the typical course: vomiting followed by irritability, seizures, and sometimes coma. Treatment is symptomatic and prognosis is unknown. Physicians who care for children should be aware of the potential toxicity of gamma benzene hexachloride since other agents also are available for the treatment of scabies in infants and young children.

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Office Treatment of Large Ischiorectal Abscesses

EVEN LARGE ABSCESSES can be treated in the office with a few milliliters of a local anesthetic to allow a small stab wound to be made into the abscess and to allow its drainage. Mushroom catheters are soft latex rubber and therefore some attention should be given to the size of the mushroom portion of the drain as well as to the size of the incision so that it will be held snugly. The mushroom portion is stretched over a probe or a small instrument so the incision need not be so big as to accept the mushroom portion of the drain as it normally rests. . . . If we give some thought to availability of beds and immediacy of repair, maybe an emergency admission, a bed in the hall perhaps, waiting a few hours for an anesthetic, or a stomach to empty so that an anesthetic can be given, using wide slashes in these abscesses and lots of packing—the alternative approach of a small stab wound in the office to drain the abscess with insertion of a mushroom catheter has a great deal to offer.

—FRANK L. WEAKLEY, MD, *Cleveland*

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

The Abortion Crisis

To the Editor: In a six-to-three opinion, the United States Supreme Court recently (June 1977) ruled that the Constitution and the Social Security law do not prevent states from refusing to pay for nontherapeutic abortions for poor women.

We must face reality. In recent years some 1½ to 2 million abortions occur every year in the United States, and no amount of birth control education, free clinics or new techniques have altered this situation.

Thus, from a health viewpoint, poor women must now seek help from backroom abortionists and can end up with problems and either die or be crippled for life—the latter being very expensive to Medicaid, which pays for the care of these ill, at great cost. One very sick patient in intensive care can cost the government $20,000 to $30,000—enough to pay for 100 to 150 abortions at $200 each.

Before the legalization of pregnancy terminations, illegal abortions constituted the leading cause of maternal deaths. How many there were is purely conjectural, for only since 1974 has accurate reporting for all states been established. As an example, in New York City alone there were reported 25 to 35 criminal abortion deaths in each of the five years immediately preceding 1970. Thus those that occurred throughout the country had to be in the hundreds each year. Taking statistics from the April 1977 issue of *Abortion Surveillance,* published by the United States Department of Health, Education, and Welfare (DHEW), during the year 1975 there were four illegal abortion deaths throughout the country. In 1976 New York state reported there were no such deaths. In an *OB-GYN News Bulletin,* July 1977, Dr. Edelin of Boston cited data from a Georgia study, which he said showed 88 percent of the deaths from illegal abortion in that state were poor black women.

To be more specific regarding economics and costs: the price of an abortion is approximately $200 through Medicaid; the cost of having a baby is about $1,100, unless a cesarean section is done (now some 18 percent of all deliveries[1]), then Medicaid picks up a tab of close to $1,700. This is just the beginning. For the next 18 years there will be problems with these unfortunates. The cost to the public skyrockets to more than $1,000 per year per child, perhaps to $2,000 (more, if the child is abnormal), or an average of some $1,500 per year for 18 years, or $27,000 per nonabortion.

In 1976 Nevada Medicaid spent $80,000 on abortions at approximately $200 per case. This meant about 400 abortions. If these same patients were to have had their babies and were to stay on welfare for 18 years, the cost would be, at $27,000 each, $10,800,000. This is just for Nevada, the 46th state in total population.

Throughout the country an estimated 300,000 women will be left without means of a free abortion, according to DHEW. This would cost the country $60,000,000 (same as published for 1976), a small pittance compared with 300,000 multiplied by $27,000 over the next 18 years, equaling $8,100,000,000. This, unfortunately, spells out only the partial cost of unwanted children, since 60 percent to 80 percent of boys from indigent families on welfare will be arrested for a crime by the age of 18, and an equal percentage of girls will become pregnant by the age of 16, the latter further swelling the welfare rolls—and making necessary more schools, courts, police, fire protection, jails and, of course, additional medical facilities.

Economists are rightly asking now, "What happens when the workers, the producers, are outnumbered by the recipients, the unemployed, the aged, the invalided, the indigent?" This trend toward Robin Hoodism is already expanding too fast—it cannot last.

"Famine and mass starvation loom over Asia, Africa and Latin America where millions of people may soon breed themselves to death," to quote University of California Food Task Force scientists. Why should we willfully follow their trend?

What prompted the Hyde Amendment (which disallowed federal funds to be used for elective abortions); what was behind it? Certainly it was not an economic measure—we have shown this quite clearly. One might conclude that its acceptance was necessarily based upon moral, political or religious grounds, or a combination of these. As to the latter, those who feel strongly about the issue of never aborting a fertilized egg have this right, of course, for themselves, but for themselves only. The rights and opinions of others deserve respect, too.

Is it moral to force a poor woman to search for an inexpensive and often an ineffective abortion with its complications, or to bear an unwanted child, thus tying her to prolonged welfare? Would it not be more humane and understanding to get her on and then off welfare, providing her with safe care in the meanwhile? In most instances, as Justice of the Supreme Court Thurgood Marshall stated, "This new law will 'brutally' coerce poor women to bear children," and he was "appalled at the ethical bankruptcy of those who preach a 'right to life' that means a bare existence in utter misery for so many."

Fortunately, quite recently, during the first week of August, the Senate decreed that abortions would be permitted with federal funds to save the life of a mother, or if her health were in actual jeopardy. Had the Senate gone along with Hyde and the lower House, it would have been a death blow to the progress of medical science and to the welfare of poverty-stricken ill, a blow by a weighty crucifix molded of antiquated, religious orthodoxy in a cauldron of political high jinks. Words are not to be found that condemn strongly enough this totally unacceptable view, for life and health are our most precious possessions.

For the record, this writer is, and always has been, in favor of amply assisting those who are in dire straits, those who are in need.

SOL T. DELEE, MD
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The Policy Lessons Learned From RMP

TO THE EDITOR: A preliminary report, "The Lessons Learned, The Regional Medical Program (RMP) Experience,"[1] has been prepared by the Health Policy Analysis and Accountability Network, Inc. (HPAAN) of Boise—understandably they would have you pronounce it "happen." This organization seems to be attempting some kind of "cost-effectiveness" assessment of the ten-year Regional Medical Program. They only partially succeed.

Rather than actually grappling with that problem, the HPAAN survey attempted only to assess the value of the program from the standpoint of its structure and the success or failure of its function. In short, the survey was concerned with how the program worked, and what could be learned that might help in shaping future "health planning and health resources development" programs.

A practicing physician, plowing his way through the report of this "opinion survey" is puzzled by the fact that in searching for information on the value of Regional Medical Programs, HPAAN sought out the views of so few grass-roots "health care providers." Only 7.6 percent of the list of 297 respondents were in private practice. All the others were drawn from the ranks of health planners, administrators, researchers, educators, government officials. Were we, the "consumers" of these regional medical programs, too close to the project to allow proper perspective?

It was inevitable, then, that this analysis of the RMP experience would be of lesser interest to physicians and nurses than to health planners. The thrust, repeatedly emphasized, was to find "implications for future health policy." That, in itself, should make us prick up our ears and listen. What more might the health planners have in store for us?

Some of the recommendations made were moderately reassuring. HPAAN's report suggests that

> . . . the primary federal role in the development of health resources should be a role of stimulation—of providing start-up funds for demonstration projects, assisting in the education and distribution of health manpower, for example, and other kinds of support activities.

They hasten to add that this should be by no means a "federal giveaway program." The government must maintain control. Nothing new about that. If the government funds a project it reserves the right to pull the rug out from under it.

The report goes on to suggest that "regardless of the federal role in a program, the actual programming at the community level must include community involvement if the effort is to be successful." That involvement, of course, includes

physician cooperation. During the ten-year lifespan of RMP, many of our colleagues were somewhat less than enthusiastic in their cooperation, possibly with good reason.

Another fairly obvious observation was that to produce an effective program there must be careful planning and strong leadership. The success of the Emergency Medical Services Program was cited as a case in point. Most of us will agree that this piece of legislation, at least, was "implemented in an orderly manner which allows for sufficient time for planning and requires evaluation as a part of the programming effort." But here we are dealing with objectives more tangible, more measurable than, say, the continuing medical education of health professionals, and its hoped-for impact on patient care.

The innovations in patient care, the technological triumphs that were presented as a part of the RMP educational programs, were commended by the report. The analysts contend that, regrettably, these were directed at the wrong end of the health care system, at the tertiary level of highly specialized treatment rather than at the primary care level where the need was far greater. And, too often the news of these brilliant technological achievements would filter down through the media to the public, creating ever greater expectations and increased demand, with resulting spiraling of costs. Every hospital worth its salt would now have to have a costly coronary care unit.

We taxpayers who foot the bill for such projects as RMP's could take some solace from several of the other recommendations made by the analysts at HPAAN. In commenting on the usual practice of three-year funding, HPAAN suggested that "It appears much more realistic and productive to authorize a program for a five-year period initially and then review the results and extend the project for one to three years based on the progress during the first five years." That seems reasonable. But just how will that assessment be made, and who will make it?

They insist, moreover, that there must be a "need for consistent policy if programming is to be effective. . . . Projects are planned and never initiated, other projects are planned and started but not continued and still others are planned and started and continued for a while only to be dropped before other sources of continuation funds can be identified." Any of us who has had experience with federally planned and funded programs can say amen to that.

One of the most controversial aspects of the Regional Medical Program, and one only briefly commented on in the HPAAN analysis, was the fact that it was regional. In the original RMP legislation, and in the law that followed it, namely the National Health Planning Resources Development Act, the Secretary of Health, Education, and Welfare has the power to overrule state governments. If we look at this closely we discern that the 19th century battle about states' rights has been declared anew.

Moreover, in some states, certainly in Idaho, the concept of regionalization produced confusion through overlapping programs, and in a few instances a rivalry and hostility that was of no benefit to the people whom the program was designed to serve. It would seem that in some quarters this federal program, conceived and dedicated to the proposition of wiping out disease, was looked upon as an invidious plot to bring regionalization to us through the back door.

Others will continue to wonder at the naiveté of a Congress that established the Regional Medical Programs, frequently "based in a third sector area, [neither public nor private sectors] in which they had commitments to work with the private sector to bring about change voluntarily but also had to maintain accountability for use of public dollars." From the start it should have been obvious that the government just could not bring this about.

Of course, the avowed purposes of our RMP to improve the health care of the American public, to increase access to health care and to possibly reduce the cost of health care fell far short of these goals. Whether there was an upgrading in the expertise of any of the practitioners touched by the program is a question that was not answered in the report.

For all the millions of dollars spent, does not the American taxpayer have a right to expect some proof of value received? And nowhere in this lengthy dissertation called a "Preliminary Report" are we told who authorized this study, or who paid for it. Many practicing physicians who participated in these programs would have been only too happy to offer a honest appraisal, for free.

The Regional Medical Program died a lingering death. We now have with us a somewhat less boisterous offspring, hatched by a mother-hen Congress. This young, 3-year-old legislative child called "The National Health Planning and Resources Act" has already begun to flex its muscles and to show its strength. At this point the Ameri-

can public can only hope that close attention will be given to what happened at HPAAN when "297 leaders among the Nation's health interests," as the report characterizes the survey respondents, wrote the RMP epitaph.

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Drug Abuse and Detoxification

TO THE EDITOR: Thank you for the four pages dedicated to substance abuse in the July 1977 issue of WESTERN JOURNAL (Notes on Alcoholism and Drug Abuse).

If I am included in your "consensus of practicing physicians," I must protest. The statements were fine as far as they went, but in an effort to make the statements simple or because of publishing restrictions, you have left out important facts that need to be available to every physician confronted with these problems.

First, in relation to phencyclidine (PCP): It is seldom the sole drug of abuse. Often the patient has a long previous history of glue sniffing or amphetamine abuse, up to 10 grams a day taken intravenously for months, or barbiturate abuse of 2 grams per day or months of chronic alcohol consumption to drunkenness. Each of these abuses may bequeath important medical problems to the PCP user. More important a large number of the heroin addicts I treat have abused PCP in the past —almost 1,000 out of 3,500 different heroin addicts I have studied. More important still, many PCP addicts are already abusing heroin and cocaine when they first come to the attention of a physician.

In regard to the use of propoxyphene napsylate (PN) (Darvon-N®) in detoxing, I agree entirely with the article as far as it goes. However, based on an experience with more than 6,000 separate detoxifications, a third on methadone, two thirds on PN, I would warn that many heroin addicts should not be detoxed as outlined.

Heroin addicts can be easily grouped into "junkies" who need routine detox (about half of those seen); addicts so depressed, even suicidal, that the depression must be treated before they can safely be detoxed; addicts so gripped by the acute anxiety syndrome that they need massive reassurance and placebos so that routine treatment would be a disservice; addicts who are out to manipulate the physician for the sake of manipulation. These "Baron Munchausens" are well known in the medical literature but only recently have we been able to appreciate how devastating they are to detox programs.[1] Individual physicians willing to use any detox schedule on a heroin addict must be prepared to take into account the special considerations needed for preventing suicide, purposeful nonsuicidal overdose or fraud.

Physicians who are not willing to treat substance abusers need a good incidence figure to judge for themselves how many of their patients are occult abusers or disguised abusers with multiple habits. For example, most alcoholics who also abuse heroin or PCP cannot get treatment from programs or from private physicians unless they hide the use of one or more of their other drugs. Most alcoholics who are suicidal cannot get treatment from alcoholism programs and most heroin addicts who are suicidal cannot get treatment from heroin programs unless they hide their suicidal tendencies—all this at a time when they very much need to talk about their depressions. In Alameda County, California, about one in 20 adults who might go as patients to practicing physicians have some problems with heroin, three of 20 adults have enough problems with alcohol to be of concern to their physicians (Hayward O: Unpublished data).

We do a disservice to private physicians unless we emphasize that most substance abusers have complex problems and that more than a third of them are seriously depressed.

Further, I would quarrel with the amount of PN suggested by Rossiter. For six months I have been using the following successfully in ambulatory addicts: PN, 600 mg per day for seven days and diazepam (Valium®) 30 mg per day and chloralhydrate, 1 gram per day with a vigorous hydrotherapy schedule with fluid and potassium replacement. They must understand that for two or three days they will feel as ill as with the grippe. In these circumstances 80 percent of heroin addicts have a good detox with most taking the next step toward rehabilitation. Most of our failures were among those with severe acute anxiety, often with minor addiction.

A minor point in Dr. Hayes' article—it is not enough for the physician or his nurse to stand at the bathroom door and stare at the patient's back as the urine is passed. Addicts are skilled in unbelievable subterfuge by years of urine testing in

the criminal justice system. "Personal supervision of the patient" means the urine is watched going from urethra into the bottle and the bottle, still warm, is handed to the watcher.

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* * *

Dr. Rossiter Responds

TO THE EDITOR: The letter from Dr. Hayward deserves a response. I refer to his comments relative to the use of propoxyphene-napsylate (PN) in the use of heroin detoxification.

There is no disagreement with the dose range suggested by Dr. Hayward for PN in detoxification of heroin addicts and as it is combined with other medications. The article in the WESTERN JOURNAL stated that "many physicians are at present prescribing the drug at high doses [higher than those specified in the package insert]—and at low doses in combination with target symptom medications." The dosage specified in the article at 800 to 1,200 mg per day and tapered to zero in 5 to 21 days is the dose range being used in those experimental projects approved by the California Research Advisory Panel. The article presents guidelines, but in a perfunctory manner. I suggest that Dr. Hayward and others interested in further exploration of this subject should read the proceedings of a symposium on the investigational use of PN in the treatment of narcotic dependency.[1]

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Concerning Libraries in Smaller Hospitals

TO THE EDITOR: Hospitals of all sizes need library services to provide up-to-date information for physicians, to support continuing education programs, and to meet the standards of the Joint Commission on Accreditation of Hospitals and the applicable state codes (in California, the California Administrative Code[1]).

A small community hospital neither needs nor can afford the facilities and services of a large university affiliated research oriented metropolitan hospital.[2] Nevertheless, the common practice of designating as a library a conference room or physicians' lounge with bookshelves crammed with outdated medical textbooks and old journals, together with a few purchases of *Current Therapy,* is clearly inadequate. The essence of a useful library is the organization of the material to make it accessible, and the provision for access to information that is not in the library but is available elsewhere. This can be provided through the services of a professional medical librarian.

Various methods for providing such professional library services to small hospitals have been reported.[3-5] In contrast with these programs, which are affiliated with institutions in large medical centers, three small acute-care hospitals in the vicinity of the San Francisco Bay area are providing quality medical library services at little cost by contracting with an independent consultant who works a few hours a week at each hospital. Doctors' Hospital of Pinole (137 beds), Vallejo General Hospital (99 beds) and Intercommunity Hospital in Fairfield (80 beds) are small, acute-care general hospitals about 20 miles apart and 30 to 50 miles from San Francisco. Each of the hospitals has set aside a room to serve as a library in accord with Title 22 of the State of California Administrative Code, but the "libraries" were much as described above.

Thus, the librarian's first task was to identify the books that clearly should be retained and make recommendations to the library committee concerning the disposition of the balance. The retained books were catalogued and classified, and recommendations were made to the library committee for first and second priority purchases to assure an adequate core library. In addition, special subject sections were developed to support the clinical departments of each hospital. For example, Doctors Hospital of Pinole has a total body scanner and no obstetrics department; Vallejo General Hospital has strong respiratory and physical therapy units; Intercommunity Hospital has active obstetric and pediatric departments. The collections at each hospital reflect these differences.

The essential minimum service provided by the consulting medical librarian is the organization and maintenance of the library so that current information is available and can be found readily. The most valuable contribution which the librarian can make to patient care is the provision of reference services to the doctors.

A physician treating a patient with an uncommon illness at one of these small hospitals can have access to useful literature essentially equal to that available to a physician in a large metropolitan hospital. An experienced, professional librarian with friendly relationships with librarians in the larger hospitals in the area can provide needed information rapidly upon demand. Access to Medline is particularly helpful. The consulting librarian can be contacted at whichever hospital she is attending that day and the requested reference research can begin immediately. The basic reference tools are available at each hospital and urgently-needed information is obtained by telephone; this service can be made available full-time by a part-time consultant to several hospitals.

In addition, the librarian reviews a variety of journals and copies articles of interest to specialists published in journals they do not regularly read.

Small hospitals cannot afford a complete medical library. They can, however, afford a core library and the prompt, efficient and relevant library services of a consultant medical librarian.

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Lithium-Carbonate-Induced Hypercalcemia

To the Editor: Lithium carbonate is an effective and commonly used drug for the treatment of cyclic manic depressive illness. Numerous adverse effects have been well-documented; however, they are seldom encountered at serum lithium levels below 1.5 mEq per liter. Diabetes insipidus, euthyroid or hypothyroid goiter, cardiac arrhythmias, ST and T wave abnormalities, anorexia, diarrhea and vomiting, neuromuscular irritability, and ataxia are the most commonly encountered side effects. A less frequently recognized long-term side effect of lithium carbonate therapy is hypercalcemia. In 1973 Garfinkel and co-workers[1] described a case in which hypercalcemia and primary hyperparathyroidism may have been related to lithium carbonate therapy.

Recently I had the opportunity to study a 63-year-old man with a long history of manic depressive illness. He was first seen in the Mental Hygiene Clinic, Veterans Administration Hospital, Roseburg, Oregon, with a typical history of manic depressive illness with several episodes of mania. Following initial evaluation, the patient was started on a regimen of lithium carbonate, 600 mg twice a day. Two weeks later he was reevaluated and was doing well clinically and his serum lithium level was 0.8 mEq per liter. Other laboratory tests were all within normal limits.

The patient was followed at periodic intervals ranging from one to three months for the next year. Fourteen months later the patient became irritable, had motor hyperactivity, lack of memory, insomnia, poor judgment, aggressiveness toward the family, and episodes of confusion and disorientation. A history of increased thirst, dry mouth and constipation was also obtained. On this occasion all laboratory tests were within normal limits except for a serum calcium level of 11.5 mg per 100 ml with a total serum protein value of 6.9 grams per 100 ml. He was admitted to hospital and treatment carried out with orally given fluids and furosemide. On the third hospital day the serum calcium level was 12.7 mg per 100 ml and treatment with intravenously given fluids and furosemide, 80 mg twice a day, was initiated and the lithium carbonate therapy was discontinued. Five days later the calcium value had decreased to 10.6 mg per 100 ml.

In the following week there was a recurrence of the manic symptoms and a psychiatric consultant recommended restarting administration of lithium carbonate. Ten days after restarting lithium carbonate therapy, serum calcium and parathyroid hormone values were obtained, at which time the ionized serum calcium level was 5.7 mEq per liter (normal range, 4.6 to 5.5 mEq per liter). Serum parathyroid hormone by radioimmunoassay was 532 pg per ml. A repeat serum calcium study four days later gave a value of 10.9 mg per 100 ml. Lithium carbonate administration was again stopped and no other therapy was given. After ten days the serum calcium level was 4.8 mEq per liter and the parathyroid hormone value was 500 pg per ml.

Christensson[2] reported the cases of six patients

treated with lithium carbonate because of manic depressive illness for two to four years; in all of these, hypercalcemia developed after an average of one year of this therapy. In our patient there was a normal serum calcium value and no evidence of hypercalcemia before institution of lithium carbonate therapy. Fourteen months later symptoms suggestive of hypercalcemia occurred together with features resembling exacerbation of his mania. The serum lithium level was found to be within normal limits; however, the serum calcium level was elevated. Attempts to treat the hypercalcemia without discontinuing the lithium carbonate therapy failed and the serum calcium level only returned to normal upon discontinuing the administration of lithium. With recurrence of manic symptoms, lithium carbonate therapy was restarted and ten days later hypercalcemia recurred with a normal serum lithium level. Measurements of serum parathyroid hormone concurrently with the serum calcium showed a level that was inappropriately high for the serum calcium, suggesting loss of feedback mechanism. Lithium carbonate administration was again discontinued and the serum calcium level returned to normal with very little or no significant change in serum parathyroid hormone level.

These cases suggest that lithium carbonate probably affects the feedback mechanism permitting parathyroid hormone to be secreted in the presence of hypercalcemia. In each of the cases reported by Christensson, a parathyroid adenoma was found at operation. It is therefore probable that these patients have an increased parathyroid gland mass and a preserved feedback mechanism under normal circumstances. However, if there is an added influence that tends to disrupt the serum calcium in the feedback mechanism, overt hypercalcemia occurs.

Since hyperparathyroidism is not a rare disease and is frequently associated with symptoms that might be confused with manic depressive illness, it is suggested that all patients receiving lithium carbonate therapy be closely monitored, having in mind the possibility of hypercalcemia and hyperparathyroidism.

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Organized Medicine's Neglect of Community Hospital Based CME

To the Editor: As the pressure for evidence of physician continuing medical education (CME) mounts, the money being spent and the energy being expended is clearly staggering. The August 1977 supplement of the *Journal of the American Medical Association* on CME indicated that more than 7,000 courses for physicians would be presented during the year 1977-1978.

What is sad about this flurry of activity is what I perceive as the improper direction it takes. For years the AMA and some state medical associations, including the California Medical Association, have issued pronouncements exhorting "on-the-site, problem-oriented learning" educational activities by and for practicing physicians within their own community hospitals based on encountered medical problems; but organized medicine falters in its interest with little in the way of active participation in and for these programs. Instead, the truly pressing educational needs of thousands of practicing physicians are met by the daily deluge of slick, high-gloss brochures advertising virtually limitless, prearranged medical programs at one of many medical centers, at registration fees of $100 to $300.

One cannot refrain from speculating as to the degree that this frenzied cornucopia of university medical programs may be prompted by the revenue-producing aspects of CME. Meanwhile, the CMA has concerned itself primarily with the inspection of participating hospitals every two years for CME certification and tabulating the physician hours of CME activity. Nobody belittles this effort, but it simply is inadequately responsive to the educational needs of the vast bulk of physicians—namely, the advancement of soundly based medical education *at the local community level.*

Many of us are firmly sold on the following concept—the most effective CME activity for practicing physicians is *community* situated, regularly planned, well directed, problem-oriented CME. Organized medicine and the academic medical establishment could be of enormous assistance in creating and supporting such programs—if they only would.

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Refer to: Kennedy D: Ten medical myths about FDA. West J Med 127:529-534, Dec. 1977

Special Article

Ten Medical Myths About FDA

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ONE OF MY first self-imposed tasks after coming to the Food and Drug Administration (FDA) was to search out better ways to communicate with the people who provide care in the health care system. In beginning that search I looked through minutes of meetings held by FDA with physicians and other health care professionals—the ad hoc professional meetings that take place throughout the country. As a result I participated in one as soon as I could.

The questions asked by physicians were of particular interest. They were serious, important, informed. Unfortunately, the information on which some of them were premised—although plausible and widely accepted—would have been more at home in the mythology of Homer than the medicine of Hippocrates.

As I became aware of the mythology quotient, I was reminded of some lines from a Yale commencement speech given by President John F. Kennedy in June 1962. After accepting his own honorary degree and observing that he now had the best of both worlds—a Yale degree and a Harvard education—President Kennedy pointed out that ". . . the great enemy of truth is very often not the lie—deliberate, contrived and dishonest—but the myth, persistent, persuasive and unrealistic."

Real communication between the medical profession and FDA depends upon exorcising several myths about the regulatory process. These myths are pernicious as well as persistent, for they divert the free flow of understanding between those who deliver health care and those who seek to support their efforts.

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Myth Number One. *Drug labeling is FDA's way of telling physicians exactly what they can and cannot do with prescription medicines, and physicians who prescribe for unlisted indications are violating the law.*

Myth Number Two. *In those instances where there is widespread prescribing for an indication not specified in the labeling, FDA seems unwilling or at least insensitive to the need to eliminate the unjustified threat of malpractice litigation by expanding the list of approved indications.*

I group these two myths together because they constitute two aspects of the same problem: myth number one involves legal *status;* myth number two concerns *process.* With regard to the first of these, the plain fact is that FDA approves the accuracy of what is on the official labeling; the physician takes it from there. He or she is responsible for making the final judgment about which, if any, of the available drugs the patient will receive in light of the information contained in the drug labeling and *other available data.*

The law requires that when a new drug is approved for marketing, the conditions of use that the manufacturer or other drug sponsor has *claimed* and *proved* must be set forth in detail in the official labeling. This labeling must accompany the drug in interstate shipment and must contain adequate information for safe and effective use of the drug, including indications; effects; dosages; routes, methods, frequency and duration of administration; contraindications; side effects, and precautions. All of this information is derived from the data submitted with the new drug application.

Once the new drug is marketed the physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert—*without*

informing or obtaining approval of the Food and Drug Administration. Although the law does not require a physician to file a notice of claimed exemption for an investigational new drug (IND) before prescribing an approved drug for an indication not specified in the labeling, or to submit to FDA data concerning the therapeutic results and any adverse reactions observed, it is sometimes in the best interests of both physician and public that these things be done.

I know that there are legitimate concerns on the part of physicians that failure to follow the labeling of a drug may be used as evidence of malpractice. Although failure to follow labeling has sometimes been cited as showing a lack of adherence to the usual practice of medicine, it is only one element among many considered by the courts—some of the others being scientific articles, texts and expert opinion. The important consideration is whether departure from approved indications is documented by a legitimate scientific rationale for such use. At this point I must say in all candor that a number of departures that have come to our attention do not appear supportable by any such rationale; to cite but three examples, the prophylactic use of antibiotics postoperatively in uncomplicated sterile surgical procedures, the gross over-prescribing of diethylstilbestrol as a morning-after contraceptive and the misuse of the amphetamines for treatment of obesity.

While there is no magic by which FDA can cause the lag between static labeling and dynamic medicine to vanish, there *is* something we can do to clarify the issue of legal status: spell out the official policy, and give guidelines concerning when it is and when it is not necessary for a physician using a drug for an unlisted indication to file an IND or investigational new drug plan. We are therefore preparing as a matter of top priority a formal policy statement that would clarify officially the legal status of package inserts and provide more specific guidelines to physicians on when an IND must be submitted if a drug is used for research purposes.

What about the other problem: FDA's failure to expand the list of indications even when, it seems, prescribing for an indication is widespread?

One example often cited in this regard is the labeling of propranolol, which was criticized for being confined to use in arrhythmias, hypertrophic subaortic stenosis and pheochromocytoma, at a time when a number of physicians had reported using propranolol with good result in other disorders, notably angina pectoris and later hypertension. When FDA approves a new indication, the law requires that we approve it on the basis of "adequate and well controlled trials" providing scientific evidence that the drug is useful for the specific indication. If the drug sponsor—or anyone else for that matter—does not submit evidence of this kind, there is simply no way we can approve such indications, and no way to flex regulatory muscle to force the sponsor to do the often expensive research necessary.

Even though a particular indication not listed on the insert is widely recognized as appropriate by physicians, so much so that failure to prescribe for it might be considered not in a patient's best interest, the drug sponsor, not FDA, has the legally designated responsibility to produce the controlled trials needed to support the new indication. In such instances, it is far better for physicians to light a candle under the drug company than to curse the darkness in FDA.

In summary, physicians should support FDA's efforts at clarification; but they should *also* monitor their own prescribing behavior carefully, because unjustifiable out-of-label prescription is, in my view, the biggest single invitation to the regulation of medical practice itself.

Myth Number Three. *Since the 1962 drug Amendments to FDA's basic law (which require proof of efficacy), a "drug lag" has been produced. This drug lag is serving to deny Americans important new drugs available in other nations with less restrictive or dilatory regulatory agencies. Further, the cost of the regulation that has produced this drug lag far exceeds the benefits that are being denied to the American people.*

American pharmacology is the most creative in the world, not least in its ability to take inert materials and transform them into brilliant slogans. Among these, "drug lag" may be the most creative. It conveys a concept of a structural, endemic hiatus between drug development and drug marketing, rather than quantitative differences in the drug approval rate between specific countries. Those who argue for the reality of the kind of regulatory climate that would account for the gap between United States and foreign drug approval rates that would affect all drugs, point first to a collection of statistics, and then hypothesize causes for them. We, in turn, produce what we consider a more accurate set of num-

bers. But such statistical tugs of war, involving parties at interest, serve only to confuse and continue the debate.

Two steps have been needed to clear the air. The first is an effort by FDA to eliminate bureaucratic inertia in the drug approval process, particularly for drugs offering high potential value. This has been undertaken, and largely accomplished. Second has been the need for an objective assessment of the drug lag issue. Fortunately, in May of this year, the *Final Report* of the most massive external investigation of FDA ever undertaken provided precisely this kind of objective study. This report, by the Review Panel on New Drug Evaluation, concluded that evidence supporting the drug lag claims is deficient in a number of important respects.

The *Report* cites two major lines of argument by proponents of the drug lag hypothesis. One stems from a study by several physicians who analyzed drugs that were not available here but were available in other countries. This study concluded that the American public had been denied significant drugs due to the costs and delays involved in FDA enforcement of the law. The *Report* finds this contention unpersuasive because "it is unclear whether the drugs referred to in these studies represent significant advances over drugs available in the United States. Moreover, insufficient weight appears to have been given to adverse reactions from drugs marketed abroad which are not available here."

The second argument revolves around a cost-benefit analysis of the 1962 Amendments by Sam Peltzman, Professor of Business Economics, University of Chicago. After applying such analytical techniques to the Amendments, Professor Peltzman concluded that they were responsible for the gross statistical decline in post-1962 drug innovations, and that the costs of drug regulation far outweighed benefits. The *Report* found major methodological and conceptual difficulties with the Peltzman approach; the critique is worth quoting at some length:

> . . . the study used consumer demand theory uncritically and assumed rational economic behavior without accounting for major imperfections in the pricing mechanisms for drugs, such as the fact that decisions to select a drug are made by physicians, not consumers, and are based largely on medical rather than economic considerations. The study also failed to account adequately for the fact that therapeutic areas may differ significantly in their states of technological development and in their trade-offs between safety and benefit. Moreover, while the study used data from the 1950's and 1960's to assess levels of drug innovation before and after the 1962 Amendments, it is doubtful that data for the 1950's should be considered indicative of the "no regulation" situation, because the late 1950's marked the end of a period of unusually active drug innovation resulting from earlier scientific breakthroughs. In addition, although drug approvals declined after 1962, data indicate the decline began earlier. Furthermore, the 1962 Amendments were implemented gradually and their full impact was not felt until the 1970's. Finally, there are important limitations on the use of cost-benefit analysis to study the impact of drug regulation, since cost-benefit analysis entails attaching monetary values to noncommercial health effects, such as death and deformities.

I would hope that we will now spend less time arguing about this particular piece of political pharmacology, and get on with the main business as rapidly as possible. That business, plainly, is to be an effective regulator of techology transfer: watching the public safety carefully, but keeping equally careful account of the foregone benefits of innovation.

Myth Number Four. *Even though there may not in fact be a drug lag in the sense that important therapies are available elsewhere but not in the United States, there is no doubt that drug development is uneven, with certain drugs being developed and made available to patients in other countries before they are marketed here. Hence, the only way for a physician to get certain drugs for patients is to send the patients overseas.*

There appears to be little realization that the way in which drugs are regulated is bound up with something far more fundamental: the way our society has decided to organize itself in regard to business and government. By congressional design, our drug laws flow from, and to a major degree support, the free enterprise system. If a new drug found to be therapeutically important in other countries is not marketed here, FDA cannot force a drug company to apply for permission to market; neither can it do the research itself. These decisions are made by industry in accordance with prevailing commercial incentives.

Dramatic stories of persons traveling overseas to get investigational drugs have left the impression that this is the only way to secure such drugs. The fact is that physicians can often get investigational drugs for their patients by referral of patients to centers where the drug is being tested. If this does not seem practical, individual physicians can also request their own IND's from FDA or from the drug sponsor for drugs that are in the final phase of clinical investigation.

Sodium valproate offers a good example of this

misunderstanding, and it may be useful to trace steps the Agency has taken to improve the availability of this drug in the United States. In November 1976, FDA advised some two dozen new drug sponsors that their products were considered likely to be either a major or a significant therapeutic advance, and that priority attention would therefore be accorded any applications for such drugs. Among them was sodium valproate. In July 1977 FDA went as far as it could under the law: it suggested that the drug's sponsor, Abbott Laboratories, submit an NDA promptly so that the application could be taken before the Agency's Neuropharmacology Drug Advisory Committee in October 1977. FDA also made it clear that, as with other important new drugs, the Agency would consider approving sodium valproate for limited indications, if that was warranted by the scientific evidence, provided that the sponsor agreed to present additional data after marketing. Abbott subsequently advised FDA that it would supply the drug to physicians with patients who have serious cases of epilepsy that may be specifically aided by the drug. Physicians with such patients should apply to Abbott for permission to study the drug under the company's IND. Such use requires the patient to follow the protocol devised by Abbott and FDA.

Myth Number Five. *FDA, through the mechanism of the patient package insert, is seeking to insinuate itself into the physician-patient relationship.*

FDA *is* committed to a much greater use of patient package inserts, a plain-language statement of why patients should follow the physician's instructions regarding certain drugs, what the drugs are intended to do, and the risks they entail as well as their benefits. I believe that such inserts are needed for many prescription drugs—not because this offers a fresh new way for bureaucrats to join in what ought to be a dialogue between patient and physician, but for the opposite reason: because it will strengthen and stimulate cooperation by the patient with the therapeutic efforts of the physician. The fact is that today health care is too often a spectator sport for the patient. What should be of intense interest is too often a matter of passive acquiescence, because the therapy is made to seem too complex and mysterious for lay comprehension. The most cursory glance at the statistics of health outcomes of cigarette smoking, obesity, lack of exercise, excess alcohol consumption—together with the epidemic of noncompliance with prescription information that has been documented by the medical literature—point to the need for people to undertake more responsibility for their own health.

One way in which an agency such as FDA can make a contribution toward dealing with this lack of knowledge, without heavy-handed intervention or large expenditures of public monies, is through better information to patients. This may be the most cost-effective form of medical education we can practice; it supports efforts by physicians, in conjunction with pharmacists and other allied health professionals, to increase knowledge and, thereby, responsibility.

Myth Number Six. *Given the nature of our economy, our legislative and legal process, and our health care delivery system, the way drugs are presently approved is probably the best way that can be devised.*

The present system of drug regulation has served us well, but it is by no means the best that can be devised. Over the years a number of deficiencies have emerged—some minor, some of basic importance. Many of these deficiencies have been brought to our attention by the medical community; others we have isolated ourselves; still others have gained the attention of Congress, or of informed critics of the way FDA operates. Drug law revision is plainly an idea whose time has come. Recommendations for improving the regulatory system made by the Health, Education, and Welfare Review Panel on New Drug Regulation, by FDA to the Administration and in congressional testimony, and through various congressional initiatives seem sure to coalesce into basic reform. There is now a detectable consensus about the direction such reform will take:

- There are likely to be changes that will permit greater flexibility in the clinical testing and marketing of drug products, particularly those entities that may represent significantly or urgently sought therapeutic breakthroughs; there will be new authority to control the distribution of particular marketed drugs, and halt their use summarily where necessary if serious and unanticipated adverse reactions appear.
- New provisions will make drug testing and marketing a more integrated and gradual process than it is today, with drugs being used in an increasingly larger number of persons who can

benefit from their effects in decreasingly sophisticated medical settings—beginning with research scientists in the laboratories and going towards family physicians in communities.

The coming revision of our drug regulatory authority will surely eliminate anomalies that confuse almost everyone. We now have a bewildering array of entities: new drugs, antibiotics, old drugs, grandfathered drugs, and others. This medicolegal smorgasbord makes neither regulatory sense nor health sense. I do not believe that the lawyers who devised it, the regulators who struggle to enforce it, or the practitioners who so often despair of diagnosing it, are happy with the present state of affairs.

Myth Number Seven. *Generic prescribing means that physicians will no longer be certain that their patients are receiving drugs of satisfactory quality, and that many will be receiving what are in effect "second class drugs."*

In carrying out the Food, Drug and Cosmetic Act, FDA must require that every dosage form of each drug be formulated and manufactured in such a way as to meet appropriate standards, and to be safe and effective. For some drug products, in addition to evidence that the products meet appropriate physicochemical standards, a necessary part of this assurance is evidence that each active ingredient is bioavailable to a uniform and acceptable degree. There can be no scientific consideration of the quality, safety and effectiveness of a drug product without consideration of the question of bioavailability.

Until comparatively recently, laboratory testing of drugs for potency, content uniformity and disintegration time was considered sufficient to ensure uniform quality for all formulations of the same drug. Experience proved that this assumption was incorrect. Such tests were not a sufficient guarantee that chemically similar drugs are absorbed to the same degree in the human body. For example, differences in formulation—due perhaps to an ingredient designed merely to extend shelf life or improve palatability—might cause one brand of tablet to be absorbed more slowly than another. Such differences in bioavailability have been encountered in a number of important drugs, but our experience shows that this problem is *not* systematically related to whether the drug was of generic or "brand" origin.

To deal with this problem, FDA issued new regulations establishing bioavailability and bioequivalence requirements for new drugs. In addition to describing methods of testing to determine bioavailability, the regulations provide for bioequivalence requirements concerning those specific drugs that have known or potential problems of bioequivalence.

Those bioavailability and bioequivalent regulations form an essential part of the Maximum Allowable Cost (MAC) program under which the government pays under the Medicare and Medicaid programs for certain generic drugs that are available from more than one manufacturer. The important point is that before a Maximum Allowable Cost is assigned to a drug, FDA *must* review all brands of the drug, and all manufacturers, to ensure that all products meet equivalent standards and that there is no regulatory problem sufficient to prevent a MAC price from being assigned.

Myth Number Eight. *FDA, according to one of the many college classmates now practicing medicine who have recently rediscovered me, is "eliminating many proven standard medications," and following a practice designed "to eliminate a medication when a particular person or committee finds it ineffective—[a policy that] will inevitably return us to the formularies of the Middle Ages."*

FDA *has* taken action to eliminate many standard medications because it cannot be shown that they are of proven effectiveness. A bit of background is in order. Both prescription and over-the-counter (OTC) drugs initially approved for marketing between 1938 and 1962 were required to demonstrate safety but not efficacy. In 1962 Congress *required* that these drugs be retroactively reviewed for effectiveness. FDA accordingly initiated an efficacy review, enlisting the best advice it could find in the process: the National Academy of Sciences/National Research Council (NAS/NRC). The NAS/NRC convened expert panels to carry out its task. The NAS/NRC Drug Efficacy Study is estimated to affect about 80 percent of all prescription drugs (most of 512 OTC drug products in the Study have been transferred to a separate OTC Drug Evaluation Project for review).

Implementation of this Drug Efficacy Study is taking place in three broad phases. In phase I, reports received from the Academy were reviewed by FDA and Initial Announcements were published in the *Federal Register* giving effectiveness classifications for all prescription drug products in the study.

During phase II, FDA puts into a final form the classification ratings of all products reviewed. Manufacturers can then submit data to FDA to support claims of effectiveness. FDA evaluates such data and publishes its conclusions. If FDA finds that the drug product lacks evidence of effectiveness for all claims, it formally proposes to remove the drug from the market, and the manufacturer may then request a hearing. If a hearing is denied by FDA, or is held and the judgment to withdraw the drug is sustained, a Final Order is published stating the reasons and withdrawing approval of the New Drug Application (NDA). As a result, unless stayed by court order, the drug must then be removed from the market.

During phase III, FDA carries out surveillance and compliance.

As can be seen from this summary, the procedure can hardly be described as insensitive to the rights of concerned parties. Indeed, the effort consumed in weighing the evidence and in touching every base necessary to ensure due process leaves me surprised that we have made any progress at all. The box score, at this writing, is as follows: of 3,482 drugs studied, final action has been possible on 2,819, of which 2,065 have been found to be effective; 754 noneffective. (If you would like the evidence regarding why your favorite drug was considered ineffective, please write to me and I will see that you get it.)

Instead of moving us back to the formularies of the Middle Ages, this process takes us in the other direction: further from the formularies of the 1860's that caused an exasperated Dr. Oliver Wendell Holmes to write that with the exception of opium, the anesthetics and a few specific remedies, "if the whole *materia medica*, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind—and all the worse for the fishes."

Myth Number Nine. *FDA animal test protocols are unrealistic, with scientifically inappropriate doses being used, for example, to test for carcinogenicity.*

We have to begin from the premise that humans share most basic biological mechanisms with other animals, and that among those mechanisms is that responsible for susceptibility to cancer. With the possible exceptions of arsenic and benzene, *all* known human carcinogens are also carcinogenic in lab animals. In the design of animal experiments, we are faced with the problem that many types of cancer in humans do not show up for 30 years or longer—by which time the small laboratory mammal, along with ten or more generations of its descendants, has passed into history. And, if we are looking for something that causes, say, a cancer in one of every 10,000 persons exposed, it will be necessary to use several times 10,000 animals in the experimental group alone. Yet an incidence of 1/10,000 is the equivalent of 23,000 new cases of cancer in the United States population. There just are not enough laboratories, toxicologists, animal handlers, money or time to do this for each of the thousands of chemicals that must be tested. So, we compensate for the shortness of the test animal's lifespan and the necessary smallness of the sample by compensating on the other end of the test equation: we increase the dose. That rationale is based on substantial experience with the form of the relationship between dose and response. Despite the impression widely held in the lay public, we are not inducing cancer by excess. In such experiments most compounds do *not* turn out to be carcinogenic.

Myth Number Ten. *FDA talks about communication but, like many large organizations, it seems to view communication as a one-way street, with all the messages going outward. For example, FDA seems to ignore observational evidence supplied by physicians.*

The FDA operates a voluntary adverse reaction reporting system and we listen eagerly—though the sounds we hear are sometimes discouragingly faint (in the United States 15 percent of adverse reaction reports come from physicians, and 63 percent from manufacturers—almost the mirror image of the situation in Great Britain). I can assure you that we pay close attention to such adverse drug reaction reports, and that we value them highly. Every single reaction report is reviewed, and there are instances in which a single report has resulted in labeling changes.

FDA is also one of the few agencies of the federal government to hold meetings with physicians and other health professionals. I intend to continue this practice; and I also urge any reader who may have a specific question about why we act as we do, or who may wish more detailed information about any of the subjects discussed in this article, to write to me directly. I will see to it that you get a straight answer.

Refer to: Cook GB: Outpatient medical records—Improvements through layout engineering (Health Care Delivery). West J Med 127:535-541, Dec. 1977

Outpatient Medical Records

Improvements Through Layout Engineering

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Dissatisfied with some functional aspects of the problem-oriented medical records used by their medical group, a committee of member physicians redesigned their office charts. Applying techniques of systematic layout planning, employed regularly as a tool of industrial engineering, these clinicians devised what they feel to be outpatient document with unique features. The resulting product forms a cohesive unit, eliminates duplication and provides many medicolegal safeguards.

DURING THE PAST DECADE increased attention has been directed to improving medical records. The primary motivation for this effort comes from recognizing that accurate documentation of clinical activities fosters more scientific, complete and logical health care.[1-8] Secondary motivations include the realization that good records may be the single most valuable asset for successful medicolegal defense;[9,10] good records may reduce human effort in conducting the search for and the retention of clinical information;[11-13] good records may simplify the work spent in meeting governmentally imposed standards.[14,15]

Several years ago our medical group, Family Health Program, Inc., adopted problem oriented medical records (POMR).[16-18] We have been satisfied with the benefits others report.[19,20] Space does not permit a lengthy description of POMR here. However, the essence of the system is separation of the patient's complaints into distinct problems. The problems are listed separately, numbered and managed uniformly according to symptoms *(subjective)*, signs *(objective)*, diagnosis *(assessment)* and management *(plan)*.

Recently our group decided to make a critical evaluation of our office charts and improve those parts that could be upgraded further. Five physicians, our chief record librarian and a business representative from the management staff were appointed to an ad hoc committee to provide information for redesign. This report describes the investigation and shows the final results. Our accomplishment may be useful to others facing similar needs.

Methods

The committee first listed all discrete parts of our extant charts. This list was not meant to log the many different printed forms constituting the current chart, but rather to identify categories of information which, in themselves, were unique and necessary parts of a complete record (Table 1).

Next the committee recorded all apparent deficiencies in each information category, as currently collected. In all, 59 shortcomings were noted. These included improper location of data, illegibility, tendency to become soiled, faulty printing, flimsy paper, legal weaknesses and maldistribution of tasks. The defects list was set aside for use later in the actual design effort.

The committee then chose to describe an ideal

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ABBREVIATION USED IN TEXT
POMR = problem oriented medical records

chart—the best interrelation of each information category. Our attack was an approach parallel to the industrial engineering of a plant layout: the designer identifies the separate activities of a manufacturing site and assigns each productive unit to the most useful physical location in relation to all others. We adapted the systematic layout planning technique of Richard Muther to our task.[21] Each member of the committee constructed a chart from a blank matrix that displayed all information categories on the abscissa and ordinate. Independently, the members identified the ideal relation of every category to each of the others and wrote a number in each intersect on the matrix—*4* if the two categories under consideration should appear, ideally, on the same page of the new record; *3* for categories located, ideally, on facing pages; *2* for categories needing to be in the same general section of the chart, and *1* for categories having no need to relate and therefore separable into remote parts of the chart.

Synthesizing all committee members' work, we developed a graphic diagram of the relationships and from that drawing designed the final structure of our new charts, Figure 1.

TABLE 1.—*Information Categories*

- Allergy/Sensitivity List
- Consultants' Reports (in-house)
- Consultants' Reports (outside)
- Family History
- Health Maintenance Activities
- Hospitalization Summaries
- Identification Information
- Immunization Record
- Insurance Papers
- Laboratory Reports
- Medication List
- Nurses' Notes
- Past Medical History
- Complete Physical Examinations
- Pathology Reports
- Problem List
- Progress Notes (primary care)
- Radiologic Reports
- Special Consents
- Surgical Operative Reports
- Telephone Messages

Results

The Progress Record is the keystone. These pages contain the physician's narrative description of how the patient's problems are recognized, named and managed. All other elements of the chart relate either closely or distantly to these progress notes.

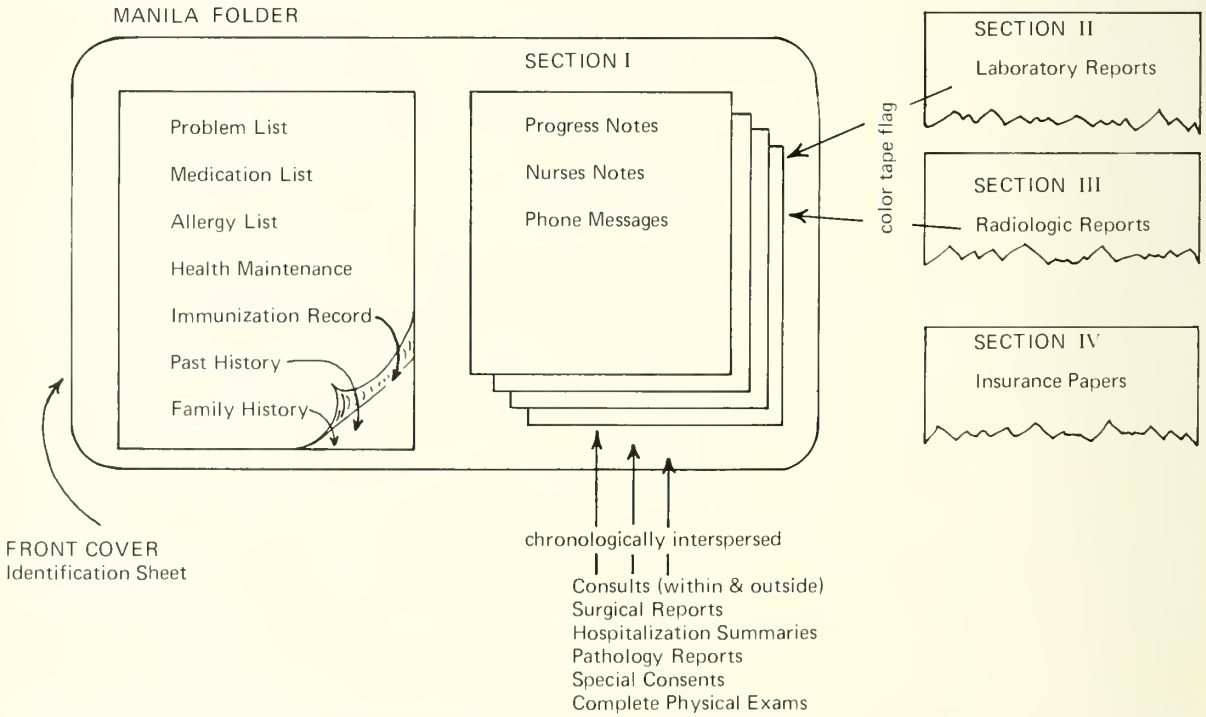
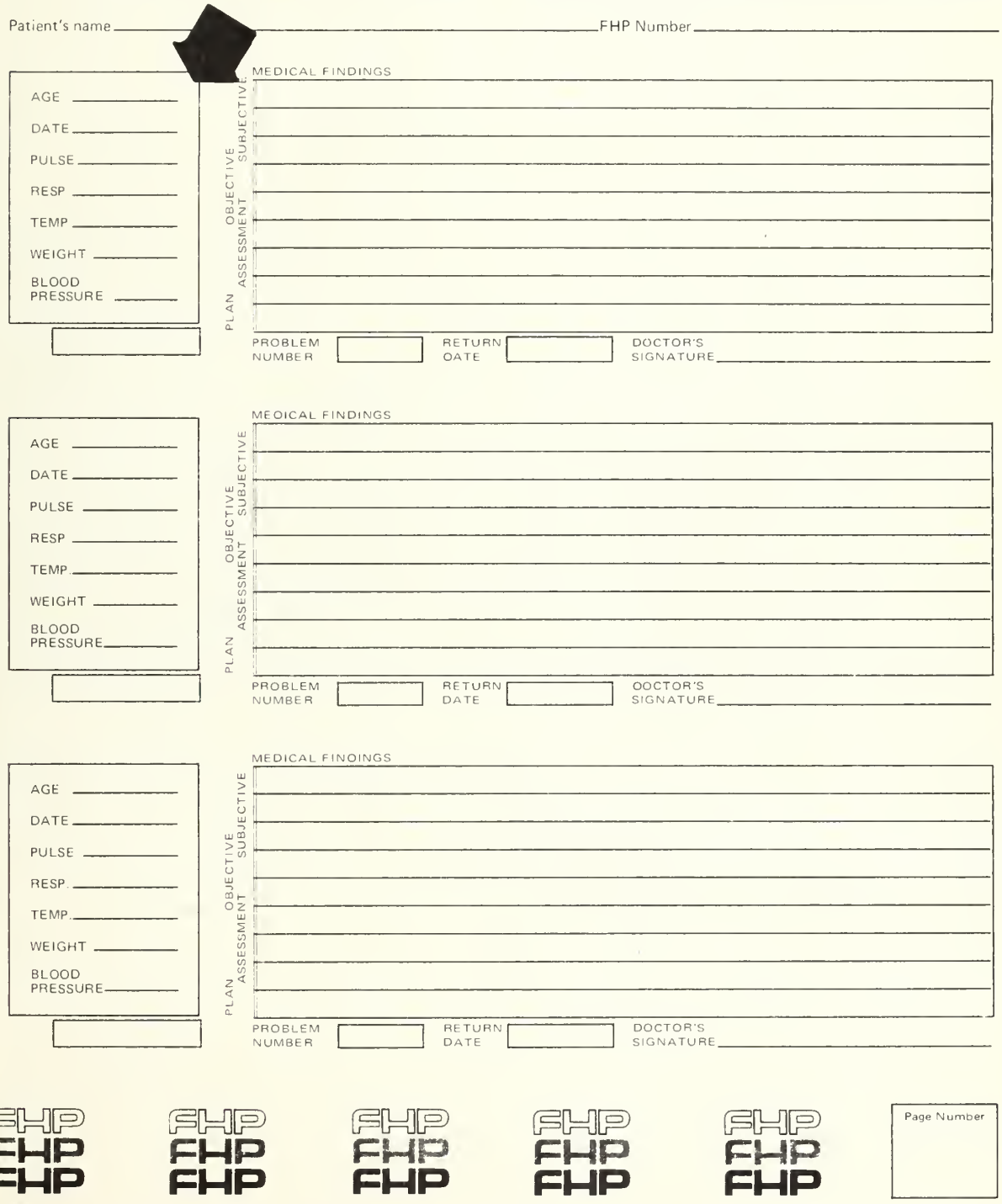


Figure 1.—The new medical chart makeup. The arrangement resulted from a study of the optimum locations for the categories of information listed in Table 1.

A frequency distribution was made to count the lines of entry used by our primary physicians for typical problem management. Reviewing 50 office visits, conducted by different family practitioners, showed the mean usage was six lines of handwritten entry. To accommodate this space requirement, but also to subtly encourage an increase in data entry, we dedicated nine lines for each primary care problem note, Figure 2. Should the primary physician need more space the narra-



FHP 2261

Figure 2.—The primary care Progress Record—keystone of the new chart. A nurses' section is marked by the arrow.

tive may continue into the next block. Following POMR precepts, each problem block is keyed on the margin with the words *subjective, objective, assessment* and *plan*. A problem number, return date and signature space complete the block. Three blocks appear on each side of each page.

To the left of each problem block is a printed box for nurses' notes with a listing of the data to be entered during each clinic visit, Figure 2 **(arrow).**

Below the nurses' section is printed a rectangle used to link the Progress Record to the Laboratory and Radiologic Sections. In classical POMR these data are entered *into* the progress notes. However, our physicians preferred to keep laboratory information and radiological reports in *separate* sections so that trends could be reviewed quickly without reading many pages of problem notes. This preference was accommodated by placing the results of these tests behind red and blue indexed section dividers lying behind the Progress Record. This modification caused a dilemma: some new test results might be overlooked. To avoid such oversight, when test results are added to the chart, a red and/or blue pressure-sensitive tag (Medi-Tags, Post Office Box 3130, Long Beach, CA 90803) is attached on the test report and also in the rectangle below the nurses' section. Therefore, immediately on opening the Progress Record, the physician is alerted that new test results are in the record. The tests are reviewed, the tag discarded and the rectangle initialed to denote *personal* attention to the new entry.

In the lower right corner of each Progress Record sheet is a space for pagination. *Every* page is numbered in ascending order. This permits accurate and swift referral back to any part and assures lawyers that the chart is intact. The convictions of our committee led us to emphasize chronological order, not just for primary care notes but for all management data. This means that the many other categories of information placed in the chart (that is, complete physical examinations, operative reports, pathology reports, consultation letters from specialists outside the group and consultation reports from specialists within the group) all enter chronologically in sequence and are numbered with the primary care notes.

All telephone messages our physicians receive from patients are written on a pressure-sensitive form, Figure 3. Its size duplicates the nine line block of the Progress Record. The message form is affixed in the chart in chronologic order and sent to the responsible physician for response. A brief entry of remarks made in the return call completes the transaction. Similar pressure-sensitive forms, each fitting neatly into the nine line blocks, are used for recording legally sensitive data describing the circumstances of patient accidents and also informed consent agreements.

A fourth indexed section, behind the Progress Record, Laboratory Reports and Radiologic Reports sections, is reserved for insurance papers and related financial documents.

The left inner surface of the chart's folder holds the Overview Record. The Overview Record is a page of heavy paper 17 by 11 inches that measures 8½ by 11 inches when folded closed. Its opening edge faces the center spine of the folder.

When folded closed it exposes the Problem List, Long Term Medication List, Allergy/Sensitivity List and Health Maintenance Activities—all in view of the practitioner writing on the Progress Record, Figure 4. The Problem List has

Doctor's Name		Date	Time	Taken By
Patient's Name	Age	FHP Number	Patient's Telephone Number (213) (714)	Time Available for Return Call From To
Incoming Message				☐ LAB RESULTS ☐ X RAY RESULTS ☐ Rx REFILL
Returned Call At	Response			

FHP 2262 Doctor's Signature

Figure 3.—The telephone message response form. This adheres by pressure sensitive gum to the nine line blocks of the progress record.

OUTPATIENT MEDICAL RECORDS

FAMILY HEALTH PROGRAM

Patient's name _____ FHP # _____ Date _____

Birthdate _____ Gender: M ☐ F ☐

	Print Problem	Date Entered	Date Resolved
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			
10.			
11.			
12.			
13.			
14.			
15.			
16.			
17.			
18.			
19.			
	SELF-LIMITED PROBLEMS		Tally frequency
20.			
21.			
22.			
23.			
24.			
25.			
26.			
27.			
28.			
29.			
30.			
31.			
32.			
33.			
34.			
35.			
36.			
37.			

LONG TERM

Medication & Dose	Problem Number	Date Started	Date Stopped

DRUG ALLERGIES/SENSITIVITIES

_____

_____

_____

_____

HEALTH MAINTENANCE

	Most Recent
Health Screen	
Pap Test	
Mammogram	
Sigmoidoscopic Exam	
Chest X-ray	
Electrocardiogram	

ENTER WITH PENCIL

Figure 4.—The Overview Record (closed)—located on the left of the open chart in constant view with the most current page of the progress notes.

MAJOR PAST MEDICAL EVENTS [Mark the years in your life these occurred]

SERIOUS Medical Diseases (by name or organ involved)

SURGICAL Operations (by name or organ involved)

SERIOUS Injuries, Fractures

DAILY USE OF

Tobacco

Alcohol

Marijuana

"Hard" Drugs

WOMEN ONLY

Pregnancies

Miscarriages or Abortions

5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80

Immunizations and Dates

TYPE	DATE	DATE	DATE	DATE	DATE	DATE
DPT.						
DT						
T						
TOPV						
Measles		Rubella			Mumps	

Skin Test

TYPE	DATE/RES	TYPE	DATE RES

FAMILY HISTORY

If any blood relatives have every had any of these conditions, please check who (If in grandparents, uncles or aunts check only whether it was on your mother's side of family or father's side of family, or both sides.)

	Father	Father's side	Brothers	Sons	Mother	Mother's side	Sisters	Daughters
Accident?								
Apoplexy (stroke)?								
Asthma, hay fever?								
Alcoholism?								
Bleeding tendency?								
Cancer?								
Cataract?								
Chicken Pox?								
Cirrhosis (bad liver)?								
Color blindness?								
Congenital heart?								
Deafness (before age 50)?								
Sugar Diabetes?								
Emphysema?								
Epilepsy (fits)?								
German measles?								
Glaucoma?								
Gout?								
Heart attack?								
High blood pressure?								
Insanity?								
Kidney disease?								
Kidney stones?								
Leukemia?								
Measles?								
Mental retardation?								
Migraine headaches?								
Mumps?								
Nervous breakdown?								
Pernicious anemia?								
Rheumatic heart?								
Stomach ulcer?								
Suicide?								
Thyroid disease?								
Tuberculosis (Consumption)?								

Write in any conditions not listed above that run in your family

If your father is alive, give his age _____ If your mother is alive, give her age _____

If any of your parents or grandparents have died, please check the age at which they died

	Under age 50	50 to 59 years	60 to 69 years	70 to 79 years	80+ years
Father died at age					
Mother died at age					
Father's father died					
Father's mother died					
Mother's father died					
Mother's mother died					

Circle the number of children born alive to your mother

1 2 3 4 5 6 7 8 9 More

Circle the number child you were in the family:

1 2 3 4 5 6 7 8 9 More

Circle the number of children you have had:

1 2 3 4 5 6 7 8 9 More

Figure 5.—The Overview Record (opened)—progress notes are immediately accessible by a simple unfolding.

an amended short section for self-limited problems and these have space allotted for keeping tally of their incidence. As the physician completes his progress note he numbers the problem box with a digit corresponding to the problem previously listed or he enters a new problem on the Problem List and numbers the problem box accordingly.

When folded open, the Overview Record gives the clinician immediate access to the Past History, Family History and Immunization Record, Figure 5. The past and family history records can be completed beforehand by the patient without professional assistance because the terminology is understandable to a layman. The past history is displayed in an unusual way, ending only at death but being useful for a lifetime. Its time-oriented feature means it can be amended repeatedly to assure that it is always current.

The final information category in the new chart is the patient identification sheet. This document contains the material that is collected regularly on any well designed hospital record frontsheet.[22]

Comment

Our new outpatient charts contain neither new nor different information, yet the arrangement is a definite departure from that usually found—an arrangement that we think is functional, legally strong and pleasant to work with. We anticipated these goals when we chose layout engineering methods to plan our design. In a sense, the efficient preparation of a complete medical chart can be compared logically to the manufacture of a piece of equipment: the historical data, the observations, the test results and the ideas that are combined to constitute proper medical care coalesce from the abstract to become a substantive product—the Medical Record.

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BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

ARTHRITIS SURGERY—Leonard Marmor, MD, Attending Surgeon, St. John's Hospital, Santa Monica, California; Lecturer, Prosthetics Education Project, University of California, Los Angeles, Center for the Health Sciences. Lea & Febiger, Washington Square, Philadelphia (19106), 1976. 548 pages, $48.50.

The author decided to change the title of his original book in 1967 from *Surgery of Rheumatoid Arthritis* to *Arthritis Surgery*. Numerous advances and contributions during the past decade in the fields of arthritis justify this increased scope.

Despite the title of the book, *Arthritis Surgery*, the author discusses the multiple facets of both rheumatoid arthritis and osteoarthritis from the standpoint of etiological and diagnostic procedures and then gives a good resume of the conservative therapeutic measures before presenting a discussion of surgery. The presence of these multiple facets well indicates, as he points out, the need for a multidisciplinary approach in the management of these complex problems, and which include collaboration with laboratory, medical, rheumatology, radiology and physical therapy personnel.

Conservative therapeutic measures for the various joints are presented, including medication, intraarticular injections, physical therapy, exercises, splints, braces and so forth. It is well pointed out that much benefit can accrue with such conservative measures and especially if such are instituted early in the course of the disease and thereby either avoid or at least considerably delay need for surgery.

Surgical procedures are discussed and, in general, well documented for the numerous joints, with known benefit or lack of it outlined based on experience and observation of different operative measures. Good discussions are given referable to contraindications for surgical operation as well as specific indications. Throughout, the author mentions important factors to help prevent postoperative infections, also—and particularly applicable in surgical procedures on the lower extremities—precautions to take to prevent thrombophlebitis and possible embolism.

The importance of careful preoperative study and particularly the psychosomatic analysis of the patient is stressed. Often patients are depressed due to increasing disability and the feeling that nothing can be done. If, on the other hand, patients, especially those with rheumatoid arthritis, can be offered even possible help by the surgeon, the personality frequently changes, depression improves and an optimistic outlook results. This increases motivation and, with good postoperative cooperation, motivation enhances success.

The author describes surgical reconstruction for joints of the upper extremities, including the hand, with both cosmetic and functional benefits therefrom, to allow the patient to feed himself, take care of personal needs and become more independent. He also reviews the several surgical procedures which offered only variable success for hip disease that were in vogue before the advent of total hip joint replacement. The latter, of course, with the use of methylmethacrylate, has had remarkable success.

There is considerable discussion about knee joint arthritis, and included are comments about intraarticular injections, including thiotepa combined with steroids, synovectomy, osteotomy for realignment of weight bearing, joint debridement and arthrodesis and patellectomy. Early joint implants with limited success are mentioned and then the author discusses some of the present knee joint replacements being used. He spends much time detailing the "Marmor Modular Knee" and with an apparent personal series of 332 cases. Such a large series would of necessity lead to enthusiasm and improved operative skill, and, with added attention to all details before, during and after operation on his part, should lead to improved results. He however records some complications with the Marmor knee. It is recognized that total knee joint replacements are far less successful than those for the hip. Compere, in *Orthopaedics Digest* (Feb. 1977), states that at least 90 different knee joints are now being studied and approximately 20 are being used routinely in individual practices.

It is obvious that further studies are necessary of implant replacements, the various materials used and fixation of these materials to bone (acrylic cement), as well as of the wear, tolerance and longevity of each and all.

The book is well written and easy to read. It includes many excellent illustrations, anatomical line drawings and photographs before, during and after operation, which add much to a better comprehension of problems, procedures and results. It is recommended for all those who are either students of, or responsible for treating, these common and difficult problems of arthritis.

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* * *

ETHICS OF NEWBORN INTENSIVE CARE—Edited by Albert R. Jonsen, PhD, Associate Professor of Bioethics; and Michael J. Garland, PhD, Lecturer in Bioethics, University of California, San Francisco School of Medicine. A Joint Publication of Health Policy Program, School of Medicine, University of California, San Francisco, and Institute of Governmental Studies, University of California, Berkeley, 1976. Send order to the Institute of Governmental Studies, 109 Moses Hall, University of California, Berkeley, CA 94720, 193 pages (155 pages, excluding notes and appendix), $4.00 (paperback), single copies free on request.

The book is a symposium based on materials presented at a conference held at the University of California, San Francisco, in May 1974. Contributors include physicians, nurses, a psychologist, a social worker, an attorney and members of the Bioethics Department of the School of Medicine.

The symposium addresses the difficult issue of life and death decisions in the context of neonatal intensive care units. It does not provide arbitrary solutions, but discusses the decision-making process from the standpoint of individual responsibility within the framework of society's concern for these decisions. The difficult decisions discussed are being made daily and this publication successfully airs the basis on which such decisions are made. Although the central role of the parents in decision-making is emphasized, no input from parents is provided. The symposium is well-written and presented in nontechnical terms. It is suitable reading for anyone interested in the process of making decisions on large issues of survival in our society. It is recommended for all persons involved in these decisions in a neonatal intensive care unit.

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CONSULTANTS FOR

The Western Journal of Medicine in 1977

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in memoriam

Anderson, A. Vance, Pasadena. Died July 2, 1977, aged 93. Graduate of Northwestern University Medical School, Chicago, 1923. Licensed in California in 1923. Dr. Anderson was a member of the Los Angeles County Medical Association.

Biskind, Gerson R., San Francisco. Died September 29, 1977 in San Francisco of cancer, aged 69. Graduate of the University of California Medical School, Berkeley-San Francisco, 1932. Licensed in California in 1933. Dr. Biskind was a member of the San Francisco Medical Society.

Findley, John W., San Mateo. Died September 26, 1977, aged 57. Graduate of the University of Chicago, the School of Medicine, 1943. Licensed in California in 1952. Dr. Findley was a member of the San Mateo County Medical Society.

Fox, Lloyd Hamilton, Bakersfield. Died October 13, 1977 in Bakersfield, aged 82. Graduate of Rush Medical College, Chicago, 1923. Licensed in California in 1923. Dr. Fox was a retired member of the Kern County Medical Society.

Giere, Carl Norman, Sacramento. Died September 24, 1977 in Yolo County, aged 70. Graduate of the University of Minnesota Medical School, Minneapolis, 1934. Licensed in California in 1943. Dr. Giere was a retired member of the Sacramento County Medical Association.

Johnson, Thomas Stanley, Upland. Died March 14, 1977 of carcinoma of the lung, aged 53. Graduate of the University of Minnesota Medical School, Minneapolis, 1952. Licensed in California in 1957. Dr. Johnson was a member of the Los Angeles County Medical Association.

Kilk, Maert, San Francisco. Died October 24, 1977 in San Francisco of heart disease, aged 49. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1955. Licensed in California in 1956. Dr. Kilk was a member of the San Francisco Medical Society.

Need, Omar U., jr., Campbell. Died August 14, 1977 in Campbell, aged 71. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1933. Licensed in California in 1935. Dr. Need was a retired member of the Santa Clara County Medical Society.

Osmon, Kent Lamar, Los Angeles. Died September 23, 1977 in Los Angeles of acute hemorrhagic pancreatitis, aged 48. Graduate of the University of Southern California School of Medicine, Los Angeles, 1954. Licensed in California in 1955. Dr. Osmon was a member of the Los Angeles County Medical Association.

Parrott, John Hugh, Santa Monica. Died July 29, 1977, aged 70. Graduate of the University of Arkansas School of Medicine, Little Rock, 1936. Licensed in California in 1947. Dr. Parrott was a member of the Los Angeles County Medical Association.

Pasette, Samuel Edward, Los Angeles. Died September 24, 1977 in Los Angeles of heart disease, aged 81. Graduate of Washington University School of Medicine, St. Louis, 1919. Licensed in California in 1929. Dr. Pasette was a member of the Los Angeles County Medical Association.

Petersen, Roy Alvin, San Jose. Died September 2, 1977 in San Francisco of complications following a surgical operation, aged 63. Graduate of the George Washington University School of Medicine, Washington, DC, 1943. Licensed in California in 1962. Dr. Petersen was a member of the Santa Clara County Medical Society.

Pinto, Harvey Elmore, San Jose. Died September 24, 1977 near Lake Tahoe of heart disease, aged 69. Graduate of the University of Nebraska College of Medicine, Omaha, 1931. Licensed in California in 1932. Dr. Pinto was a member of the Santa Clara County Medical Society.

Railsback, Oscar Caleb, Woodland. Died August 22, 1977, aged 78. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1927. Licensed in California in 1927. Dr. Railsback was a retired member of the Yolo County Medical Society.

Romm, May E., Los Angeles. Died October 15, 1977, aged 85. Graduate of the Medical College of Pennsylvania, Philadelphia, 1915. Licensed in California in 1938. Dr. Romm was a member of the Los Angeles County Medical Association.

Smart, William R., San Rafael. Died October 9, 1977 in San Rafael, aged 62. Graduate of the University of Virginia School of Medicine, Charlottesville, 1939. Licensed in California in 1946. Dr. Smart was a member of the Marin Medical Society.

Vollmer, Albert M., San Francisco. Died February 11, 1977 of myocardial infarction, aged 81. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1924. Licensed in California in 1925. Dr. Vollmer was a retired member of the San Francisco Medical Society.

Wallerius, Raymond M., Sacramento. Died September 10, 1977 in Sacramento, aged 76. Graduate of the Creighton University School of Medicine, Omaha, 1924. Licensed in California in 1926. Dr. Wallerius was a retired member of the Sacramento County Medical Association.

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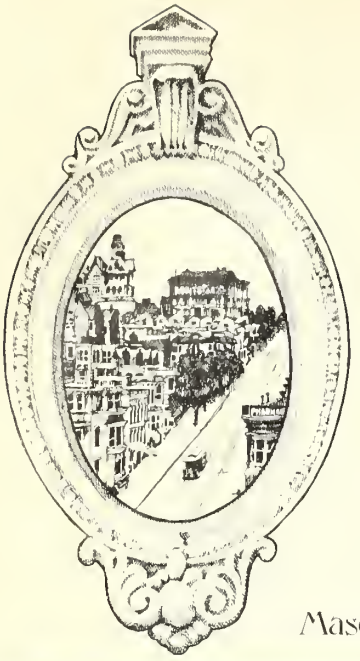

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PROGRAM HIGHLIGHTS

FRIDAY, March 17

Among the programs: family practice seminars; disaster planning with practical application; clinical review of neck and upper extremity disorders and the regional meeting of the American College of Physicians, Northern California Chapter (2 days).

SATURDAY, March 18

Ten scientific and practice sessions including pulmonary infections; adolescent gynecology; hormones and cancer in the female; hyperalimentation; pediatric intensive care; hepato-biliary imaging; updates on neurology and neurosurgery; and a chance to "Tell It to the FDA." House of Delegates opens.

SUNDAY, March 19

Offers a choice from 17 programs—some solo, others with interspecialty appeal—sponsored by the Sections on Allergy, Otolaryngology, Ophthalmology, Physical Medicine, Industrial Medicine, Neurology, Psychiatry, Pediatrics, Dermatology, Plastic Surgery, Urology and Preventive Medicine. And annual meetings of four specialty societies.

MONDAY, March 20

Social problems are addressed in courses on sexuality; death; impairment in physicians, and government's role in medicine. There also will be clinical discussions on nuclear bone imaging, laboratory and radiologic aids to understanding diagnosis and treatment, and clinical pharmacology for the practitioner.

TUESDAY AND WEDNESDAY: The House of Delegates continues.

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CMA Annual Session, 731 Market Street, San Francisco, CA 94103

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Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude development of ataxia, oversedation or confusion (not more than two capsules per day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacologic effects of agents, particularly potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

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Morning lectures will review important principles of chemistry and biochemistry and will deal with molecular mechanisms of drug actions; routes of administration; drug distribution, elimination, and time course of drug action; cyclic AMP and drugs; toxicity, tolerance and physical dependence; teratogenesis; mechanisms of antibiotic resistance; drug interactions; the F.D.A. and drug development in the United States. Afternoon informal seminars will deal with topics pertinent to pharmacology and review in detail new developments in rapidly changing fields.

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General lectures will cover a review of chemistry and physics for clinicians, chemical bonds of biological importance, subatomic particles, correlation of cell structure and function, the structure and function of proteins, sugars and lipids, the structure of nucleic acids, DNA synthesis, expression and organization of genetic information, regulation of gene expression, gene manipulation, carbohydrate and fat metabolism, bioenergetics, molecular aspects of visual excitation, the organization and function of the brain, exploration of Mars.

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Tuition fee is $275, payable with a $125 room deposit to Stanford upon application for enrollment. Acceptance of enrollment assures firm hotel reservations with choice of type of room at prevailing Mauna Kea rates. Early application is advised.

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The present knowledge of the pathogenesis of cancer and clinical aspects of diagnosis, classification, staging, and management of malignant disorders will be reviewed in this course, which is intended for all physicians and surgeons who deal with problems related to neoplastic disease. Tuition: $265.

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CANCER

January 21—**Gastrointestinal Cancer.** SF Regional Cancer Foundation at Fireman's Fund Building, San Francisco. Saturday. 4 hrs. $15. Contact: Norma Schlager, SF Regional Cancer Foundation, 14th Ave. and Lake, San Francisco 94118. (415) 221-2132.

January 25—**Breakthroughs in Lymphomas and Leukemias.** Hospital of the Good Samaritan, Los Angeles. Wednesday. 7 hrs. Contact: J. S. Bonorris, MD, Dir., Hematology Oncology, Hosp. of the Good Samaritan, 616 S. Witmer, Los Angeles 90017. (213) 488-8588.

January 27-28—**Cancer Update. A Clinical Approach to Diagnosis and Treatment of Common Malignancies—Breast, Colon, Lung and Prostate.** Peralta Hospital at Claremont Hotel, Berkeley. Friday-Saturday. Contact: Tish Hammerlee, Peralta Hosp., 450 30th St., Oakland 94609. (415) 451-4900, ext. 264.

January 30-31—**Cancer.** USC. Monday-Tuesday.

March 4—**What's New in Oncology 1978** (American Cancer Society at San Joaquin Delta College, Stockton. Saturday. 6 hrs. $20. Contact: Karen Schaefer, 1111 W. Robinhood Dr., Stockton 95207. (209) 477-2676.

March 9-12—**Modern Concepts in Oncology.** UCLA at Canyon Hotel, Palm Springs. Thursday-Sunday.

March 10-11—**Medical and Therapeutic Complications in Patients With Malignant Diseases.** Eisenhower Med. Center at Erawan Garden Hotel, Indian Wells. Friday-Saturday. 10 hrs. $50. Contact: John J. Deller, MD, Dir. of Education and Research, EMC, 39000 Bob Hope Dr., Palm Desert 92260.

March 10-12—**Cancer Endodurietherapy.** USC at Hotel Bonaventure, Los Angeles. Friday-Sunday. 22 hrs.

March 17—**Cancer of the Lung.** California Hospital Medical Center, Los Angeles. Friday. 5 hrs. $15. Contact: Kenneth L. Senter, MD, Dir., Med. Ed., CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411, ext. 251.

March 27-31—**Cancer.** STAN. Monday-Friday. 27 hrs. $265.

May 10—**Carcinoma of the Cervix: Diagnosis and Treatment.** LLU. Wednesday. 4 hrs. $25.

EMERGENCY MEDICINE

January 23-27—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Town and Country Convention Center, San Diego. Monday-Friday. 40 hrs. $325.

January 23-27—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

January 30-February 3—**Emergency Medicine.** UCLA at Beverly Hilton Hotel, Beverly Hills. Monday-Friday.

February 26-March 3—**Emergency Medical Care Symposium II.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday. $175.

March 20-24—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday. 40 hrs. $325.

April 3-7—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $325.

April 15-22—**Emergency Medicine.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week. 29 hrs. $300.

May 8-12—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $325.

May 9-13—**Topics in Emergency Medicine.** UCSF at Ralph K. Davies Med. Center, San Francisco. Tuesday-Saturday.

MEDICINE

January 4-March 15—**Nights at UCLA: Infectious Diseases for the Practicing Internist.** Wednesdays; 7:30-9:30 p.m. 22 hrs. $200.

January 11—**Management of Arrhythmias.** LLU. Wednesday. 4 hrs. $25.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

January 13-14—**Annual Allergy Symposium.** Southern California Permanente Medical Group at Beverly Hilton Hotel, Beverly Hills. Friday-Saturday. Contact: Shirley Gach, So. Calif. Permanente Med. Group, 4900 Sunset Blvd., Room 6014, Los Angeles 90027. (213) 667-4241.

January 14-15—**Practical Pulmonary Diseases for the Primary Care Physician.** UCLA. Saturday-Sunday. 14 hrs. $140.

January 20-21—**New Developments in Stress Testing.** American College of Cardiology at Memorial Hospital Medical Center, Long Beach. Friday-Saturday. Contact: Miss Mary Ann McInerny, Dir., Extramural Programs Dept., Div. of Cont. Ed., ACC, 911 Old Georgetown Rd., Bethesda, MD 20014.

January 21—**Systemic Disease/Eye, Mouth, Skin Manifestations.** See Of Interest to All, January 21.

January 24-27—**Present Concepts in Internal Medicine.** American College of Physicians at Letterman Army Medical Center, San Francisco. Tuesday-Friday. Contact: Registrar, ACP, 4200 Pine St., Philadelphia, PA 19104.

January 25—**Venous Thrombosis and Pulmonary Embolism—Dinner Meeting/Scientific Program.** LA Society of Internal Medicine at LA Co. Med. Assn., Los Angeles. Wednesday. 1½ hrs. $7.50. Contact: Thomas Yoshikawa, MD, LASIM, 8530 Wilshire Blvd., No. 313, Beverly Hills 90211. (213) 659-6750.

January 25-27—**Advances in Neurology.** UCSF at Hyatt on Union Square, San Francisco. Wednesday-Friday.

January 27-29—**New Frontiers on the Relationships of Lipids, Lipoproteins and the Arterial Wall in Cardiovascular Disease.** UC Extension, Berkeley, and UCSF at Hyatt on Union Square, San Francisco. Friday-Sunday. 12 hrs. $150. Contact: Medical Symposia, Div. of Letters and Sciences, UC Extension, Berkeley 94720. (415) 642-1061.

February 3-4—**Allergy.** STAN. Friday-Saturday. $80.

February 7-10—**Your Consultant Speaks—A Multidisciplinary Course for Dermatologists.** STAN at Lake Tahoe. Tuesday-Friday. 12 hrs. $225; $100 for residents and those in training.

February 15-17—**Topics in Gastroenterology.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday.

February 23-25—**Advances in the Diagnosis and Therapy of Cardiovascular Disease—1978.** American College of Cardiology at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed. ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 3—**Diabetes Program—5th Annual.** UCD at Red Lion Motor Inn, Sacramento. Friday.

March 3-4—**Diagnosis and Management of Aphasia.** PMC at Presbyterian Hospital, San Francisco. Friday-Saturday. 12 hrs. $100.

March 6-9—**American College of Cardiology—27th Annual Scientific Session.** Disneyland Hotel, Anaheim. Monday-Thursday. Contact: Patrick Ziarnik, Dir., Annual Sci. Session Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 10-11—**Clinical Cardiology.** American College of Cardiology at Kauai Surf Hotel, Kauai, Hawaii. Friday-Saturday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 16-19—**Viral Hepatitis.** UCSF at Hilton Hotel, San Francisco. Thursday-Sunday. 26 hrs. $145.

March 23-25—**Immunology and Allergy Conference—2nd Annual.** UCSD at Hilton Hotel, San Diego. Thursday-Saturday.

March 28-31—**Consultant's Course in Dermatology—6th Annual.** UCSF. Tuesday-Friday. $250.

March 31-April 1—**Seminar on Thrombosis.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. 10 hrs. $75.

April 3-12—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. 10 days. Contact: Miss Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 3-14—**Intensive Review of Internal Medicine.** USC. 12 days.

April 12-June 14—**Nephrology for the Practicing Internist.** UCLA. Wednesday evenings; 10 weeks.

April 14-15—**Arthroscopy.** UCLA. Friday-Saturday. 12 hrs. $315.

April 19-21—**Echocardiographic Solutions to Clinical Cardiovascular Problems.** American College of Cardiology and UCLA at Century Plaza Hotel, Los Angeles. Wednesday-Friday. Contact: Miss Mary Anne McInerny, Dir., Extramural Prog. Dept., Div. of Cont. Ed., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 24-29—**American Academy of Neurology — Annual Meeting.** Bonaventure Hotel, Los Angeles. Monday-Saturday. $35, members; $55, nonmembers. Contact: Mr. Stanley A. Nelson, Exec. Dir., AAN, 4015 W. 65th St., Suite 302, Minneapolis, MN 55435. (612) 920-3636.

May 4-7—**American Society of Internal Medicine — Annual Meeting.** Hyatt Regency, San Francisco. Thursday-Sunday. Contact: ASIM, 535 Central Tower Bldg., 703 Market St., San Francisco 94103. (415) 777-1000.

May 13—**Controversies in Internal Medicine—2nd Annual.** San Jose Hosp. and Health Center, Inc., at Marriott's Great America, Santa Clara. Saturday. 6 hrs. $35. Contact: Stanley Skillicorn, MD, Dir. of Med. Ed., San Jose Hosp. and Health Ctr., Inc., 675 E. Santa Clara, San Jose 95112. (408) 998-3212.

May 16—**Common Skin Problems Seen in Office Practice.** Eskaton Colusa Healthcare Center, Colusa. Tuesday. 2 hrs. $20. Contact: Vincent C. Sansone, MD, 199 E. Webster St., Colusa 95932. (916) 458-5844.

May 19—**American Heart Association, California Affiliate—Physicians' Scientific Sessions.** Vacation Village, San Diego. Friday. Contact: Marilyn Probst, AHA, Calif. Affiliate, 805 Burlway Rd., Burlingame 94010. (415) 342-5522.

May 22-26—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday.

OBSTETRICS AND GYNECOLOGY

January 14-21—**Perinatal Medicine.** USC at Royal Lahaina, Maui, Hawaii. One week. 21 hrs. $300.

January 19-21—**Pregnancy and Hypertension.** DREW at Hyatt House Hotel, Los Angeles. Thursday-Saturday. 20 hrs.

January 26-May 25—**Recent Advances in Obstetrics and Gynecology—2nd Annual.** UCLA. Thursday evenings. 32 hrs. $310.

January 28-30—**Comprehensive Laparoscopy.** UCSD at Kona Kai Club, San Diego. Saturday-Monday. 16 hrs. $375.

February 11-12—**Obstetrical and Gynecological Forum.** LA Obstetrical and Gynecological Society at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. Contact: Ms. Dee Davis, Exec. Sec., LA Obstetrical and Gynecological Society, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

February 15-19—**Edward Tyler Symposium on the Practical Management of the Infertile Couple.** See Of Interest To All, February 15-19.

March 9-10—**Gynecological Urology Seminar.** See Surgery, March 9-10.

April 10-12—**Antenatal Assessment of the Fetus From Conception to Delivery.** UCSD at Vacation Village, San Diego. Monday-Wednesday. 21 hrs. $150.

May 6-8—**Comprehensive Laparoscopy: Current Principles and Practice.** UCSD at Hotel del Coronado, Coronado. Saturday-Monday. 16 hrs. $375.

PEDIATRICS

January 12-14—**General Pediatrics.** American Academy of Pediatrics at Kona Surf Hotel, Kailua-Kona, Hawaii. Thursday-Saturday. Contact: L. J. Nagel, Dept. of Cont. Ed., AAP, P.O. Box 1034, Evanston, IL 60204. (312) 869-4255.

January 26-28—**Troubled Youth.** See Psychiatry, January 26-28.

January 26-29—**Winter Ski and Study Symposium—3rd Annual.** American Academy of Pediatrics, District IX, Chapter 2, at Mammoth Mountain. Thursday-Sunday. $135, members; $160, non-members. Contact: Calif. Chapter 2, AAP, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

January 27-29—**Pediatric Anesthesiology.** See Surgery and Anesthesiology, January 27-29.

January 28-29—**Pediatrics for the Primary Physician: A Practical Update.** See Of Interest To All, January 28-29.

February 10—**Pediatric Otolaryngology.** See Surgery and Anesthesiology, February 10.

February 15—**Pediatric Hematology.** LLU. Wednesday. 8 hrs. Contact: Sanford Schneider, MD, A531, LLU Med. Ctr., Loma Linda 92354. (714) 796-7311, ext. 2832.

February 23-25—**Development in Infancy and Childhood—Annual Winter Meeting.** Children's Hospital Med. Ctr., Oakland, at Sahara Tahoe Hotel, So. Lake Tahoe. Thursday-Saturday. Contact: Gretchen Hayes, CHMC, 51st and Grove Sts., Oakland 94609.

February 24-26—**Recent Advances in Patterns of Infant Development: Relevance for Later Life.** So. Calif. Soc. for Child Psychiatry; Com. on Psychiatric Dimensions of Infancy, AACP; Chap. 2, ACP, at South Coast Plaza Hotel, Costa Mesa. Friday-Sunday. 18 hrs. Contact: SCSCP, 14724 Ventura Blvd., No. 604, Sherman Oaks 91403. (213) 986-8066.

March 17-19—**Combined Southern California Pediatric Postgraduate Meeting—8th Annual.** American Academy of Pediatrics, District IX, Chapter 2, at Riviera Hotel, Palm Springs. Friday-Sunday. $135, members; $150, non-members. Contact: Calif. Chapter 2, AAP, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

April 5-7—**General Pediatrics.** American Academy of Pediatrics at Century Plaza Hotel, Los Angeles. Wednesday-Friday. Contact: L. J. Nagel, Cont. Ed. Programs, AAP, P.O. Box 1034, Evanston, IL 60204. (312) 869-4255.

April 7-8—**Common Problems in Ambulatory Pediatrics.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday.

April 8-13—**American Academy of Pediatrics—Spring Session.** Century Plaza Hotel, Los Angeles. Saturday-Thursday. Contact: L. J. Nagel, Cont. Ed. Programs, AAP, P.O. Box 1034, Evanston, IL 60204. (312) 869-4255.

May 1-5—**Pediatric Review.** USC. Monday-Friday.

May 11-13—**Annual Pediatric Course.** UCSF. Thursday-Saturday.

May 13-20—**Pediatric Workshop.** USC at Royal Lahaina, Maui, Hawaii. One week. 28 hrs. $300.

May 20-21—**Neuropediatrics.** UCLA. Saturday-Sunday. 11 hrs. $165.

May 27-29—**American Academy of Pediatrics, California Chapter I, District IX.** Hyatt House, Monterey. Saturday-Monday. Contact: Martin Gershman, MD, 595 Buckingham Way, San Francisco 94132.

PSYCHIATRY

January 3-April 4—**Intensive Review Course: American Board of Psychiatry and Neurology.** UCD. Tuesdays; 7:00-10:00 p.m. 42½ hrs. $275.

January 10-March 21—**Intensive Review of Psychiatry.** USC. Tuesday evenings.

January 13-15—**Crises in Conflict—Adolescence vs Middle Age—Annual Winter Meeting.** So. Calif. and American Societies for Adolescent Psychiatry at Marriott Hotel, Newport Beach. Friday-Sunday. Contact: Arthur D. Sorosky, MD, 16661 Ventura Blvd., Encino 91436; or SCSAP, P.O. Box 24041, Village Station, Los Angeles 90024.

January 20-22—**Psychoanalytically Oriented Psychotherapy: A Retrospective.** UCSF. Friday-Sunday. 12 hrs. $45.

January 26-28—**Troubled Youth.** USC at Vacation Village, San Diego. Thursday-Saturday.

January 27-28—**Practical Psychiatry.** PMC at Presbyterian Hospital, San Francisco. Friday-Saturday. 12 hrs. $125.

January 29-February 3—**Midwinter Program in Continuing Education for Psychiatrists.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday.

February 8—**Overview of Newer Approaches for Troubled Patients.** LLU. Wednesday. 4 hrs. $25.

April 15-16—**Stress: Psychological Management.** UCLA at Santa Cruz. Saturday-Sunday.

May 19-21—**Treatment of Schizophrenia.** UCSF. Friday-Sunday.

RADIOLOGY AND PATHOLOGY

December 20—**Diagnostic X-Ray Including Cat Scans.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Chr., Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

January 16-20—**Computed Tomography.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. $295.

January 17—**Updating Radiation Therapy.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Chr., Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

January 27-29—**Los Angeles Radiological Society—30th Annual Mid-Winter Meeting.** Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Nathan Green, MD, 15107 Vanowen St., Van Nuys 91405.

January 27-29—**New Frontiers on the Relationships of Lipids, Lipoproteins and the Arterial Wall in Cardiovascular Disease.** See Medicine, January 27-29.

February 19-24—**Interpretative Enzymology.** UCSD at Sheraton Inn-Airport, San Diego. Sunday-Friday. 25 hrs.

February 21—**Clinical Laboratory Tests: Results, Clinical Application and New Laboratory Tests.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Chr., Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

March 1—**Computerized Tomography—Dinner Meeting/Scientific Program.** LA Soc. of Internal Medicine at LA Co. Med. Assn., Los Angeles. Wednesday. 1½ hrs. $7.50. Contact: Thomas Yoshikawa, MD, LASIM, 8530 Wilshire Blvd., No. 313, Beverly Hills 90211. (213) 659-6750.

March 4-5—**Diagnostic Nuclear Imaging.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday. 9 hrs. $100.

March 5-10—**Medical Imaging in the High Sierra.** American College of Medical Imaging and American Institute of Ultrasound in Medicine at Sahara Tahoe Hotel, Lake Tahoe. Sunday-Friday. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

March 6-10—**Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. $275.

March 11-12—**A Practical Course in B-Scan Ultrasound.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday. 9 hrs. $125.

April 9-14—**American College of Radiology—Annual Meeting and Categorical Course.** Town and Country Hotel, San Diego. Sunday-Friday. Contact: Ms. Sheila Aubin, Meeting Manager, ACR, 20 N. Wacker Dr., Chicago, IL 60606. (312) 236-4963.

May 10-12—**Emergency Room Radiology.** UCSF at Hyatt on Union Square, San Francisco. Wednesday-Friday.

May 12—**Radiology Symposium.** UCD at Red Lion Motor Inn, Sacramento. Friday.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 15 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY AND ANESTHESIOLOGY

January 5-7—**Anesthesia Update '78.** UCSD at Hotel Del Coronado, Coronado. Thursday-Saturday. 15 hrs. $150.

January 16-20—**Otologic Surgery—13th Annual Course.** Ear Research Institute, Los Angeles. Monday-Friday. 45 hrs. $500. Contact: F. H. Linthicum, Jr., MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

January 20-21—**Hand Injuries and Infections.** PMC at Presbyterian Hospital, San Francisco. Friday-Saturday. 9 hrs. $150.

January 21—**Ophthalmic Plastic Surgery.** Jules Stein Eye Institute and UCLA. Saturday. 8 hrs. $200. Contact: Lu Hendricks, Academic Prog. Admin., Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

January 22-26—**Ophthalmology and Otolaryngology—47th Annual Mid-Winter Clinical Convention.** The Research Study Club of Los Angeles, Inc., at Hilton Hotel, Los Angeles. Sunday-Thursday. 28 hrs. $175. Contact: Mr. Richard Pruter, Exec. Sec., P. O. Box 49412, Los Angeles 90049. (213) 879-0143.

January 27-29—**Pediatric Anesthesiology—16th Clinical Conference.** Children's Hospital of Los Angeles at Hilton Hotel, Los Angeles. Friday-Sunday. 15 hrs. $135. Contact: Wayne Herbert, MD, Children's Hosp., 4650 Sunset Blvd., Los Angeles 90027. (213) 660-2450, ext. 2262.

February 3-4—**Phacoemulsification Surgery Course.** Jules Stein Eye Institute and UCLA. Friday-Saturday. $300. Contact: Lu Hendricks, Academic Prog. Admin., 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

February 3-4—**Intraocular Lens Implantation Course.** Santa Monica Hospital, Santa Monica. Friday-Saturday. $600; $300, residents and military. Contact: Intraocular Lens Implantation Course, SMH, 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

February 5-8—**Surgical Anatomy—19th Annual Theodor Billroth Course.** LLU. Sunday-Wednesday. 32 hrs. $200.

February 10—**Pediatric Otolaryngology.** USC. Friday.

February 28-March 3—**Diagnosis and Management of Acoustic Neuromas and Skull Base Tumors.** Ear Research Institute, Los Angeles. Tuesday-Friday. 32 hrs. $400. Contact: William F. House, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

March 3-4—**Development and Management of Aphasia.** See Medicine, March 3-4.

March 8—**General Surgery Seminar.** LLU. Wednesday. 4 hrs. $25.

March 9-10—**The Orbit: Diagnostic Approaches and Management Decisions.** PMC at Stanford Court Hotel, San Francisco. Thursday-Friday. $225.

March 9-10—**Gynecological Urology Seminar.** American Urological Association at Airport Marina Hotel, Los Angeles. Thursday-Friday. 16 hrs. $180. Contact: Gynecological Urology Seminar, c/o Joseph J. Kaufman, MD, UCLA Med. Ctr., Div. of Urology, Los Angeles 90024.

March 11—**Cataract Surgery and Intraocular Lens.** Jules Stein Eye Institute and UCLA. Saturday. 8 hrs. $225. Contact: Lu Hendricks, Academic Prog. Admin., Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

March 12-17—**Anesthesiology 1978—4th Annual Winter Meeting.** Anesthesiology Educational Foundation and Calif. Society of Anesthesiologists at Mammoth Lakes. Sunday-Friday. 20 hrs. Contact: Ronald L. Katz, MD, Dept. of Anesthesiology, UCLA School of Medicine, Los Angeles 90024.

March 19-23—**International Anesthesia Research Society—52nd Congress.** Hilton Hotel, San Francisco. Sunday-Thursday. Contact: B. B. Sankey, MD, Exec. Sec., IARS, 3645 Warrensville Center Rd., Cleveland, OH 44122. (216) 295-1124.

(Continued on Page 40)

Tablets
Percocet®-5 (C II)

DESCRIPTION Each tablet of PERCOCET®-5 contains 5mg oxycodone hydrochloride (WARNING: May be habit forming), 325mg acetaminophen (APAP).

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET®-5, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET®-5 is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET®-5 should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET®-5 may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCOCET®-5 should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCOCET®-5 should not be administered to children.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCOCET®-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCOCET®-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET®-5 is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCOCET®-5 may be additive with that of other CNS depressants. See WARNINGS.

DEA Order Form Required.

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DUPONT

November 1977 EDO 148P

FOR MODERATE TO MODERATELY SEVERE PAIN

Acetaminophen with the narcotic difference

Reliable oral narcotic analgesia...

The narcotic component in PERCOCET®-5 is oxycodone, which is readily absorbed and provides dependable oral analgesia—usually within 15 to 30 minutes. Oxycodone can produce drug dependence of the morphine type and should be prescribed with the same degree of caution appropriate to the use of other narcotic-containing medications.

...aspirin free

Acetaminophen is a non-narcotic analgesic widely used for aspirin-sensitive patients. Equivalent to aspirin in analgesia, it complements the pain relief provided by oxycodone.

The usual dose of PERCOCET®-5 is one tablet every six hours, providing convenience and economy for your patients. PERCOCET®-5 is ideally suited for your patients with aspirin sensitivity, with hemostatic disturbance, with peptic ulcer or on anticoagulation therapy.

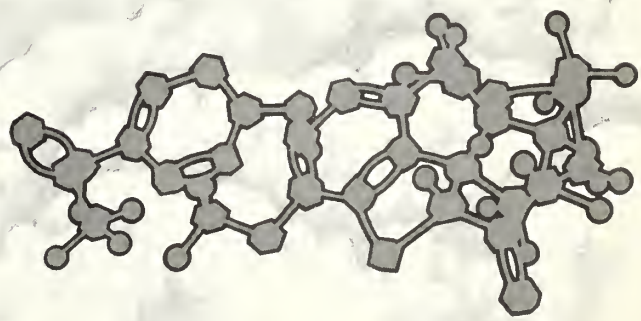
Tablets

Percocet®-5

each scored tablet contains 5 mg oxycodone HCl (WARNING: may be habit forming) and 325 mg acetaminophen

CII

When aspirin is contraindicated.



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Please see facing page for Brief Summary of prescribing information.

COLBY PROCLAIMS WOMAN SUFFRAGE

Signs Certificate of Ratification at His Home Without Women Witnesses.

MILITANTS VEXED AT PRIVACY.

Wanted Movies of Ceremony, But Both Factions Are

WASHINGTON, Aug. 26, 1920—

Social Security Bill Is Signed, Gives Pensions to Aged, Job

Roosevelt Approves Message Intended to Benefit 30,0 Persons When States Adopt Cooperating Laws-He the Measure 'Cornerstone' of His Economic Progr

WASHINGTON, Aug. 1 The Social Security Bill, p a broad program of unemp insurance and old age p and counted upon to bene 20,000,000 persons, became day when it was signed b dent Roosevelt in the pre those chiefly responsible ting it through Congress.

Mr. Roosevelt call "the cornerstone which is being me s comple ri to

SENATE APPROVES 18-YEAR OLD VOTE IN ALL ELECTIONS

Amendment to Constitution is Sent to House, Where Passage is Expected

WASHINGTON, March 10, 1971—The Senate approved today, 94 to 0, and sent to

TRUMAN CLOSES TED NATIONS CONFEREN WITH PLEA TO TRANSLATE CHARTER INTO DEEDS

NEW WORLD HOPE

President Hails 'Great Instrument of Peace,' Insists It Be Used

HISTORIC LANDMARK

Meeting Gives Standing Ovation as Executive Pictures Peace Gain

"If we fail to use it," he declared to the solemn final meeting of the delegates, 'we shall betray all of those who have died in order that we might meet here in freedom and safety to create it.'

"If we seek to use it selfishly—for the advantage of any one nation or any small group of nations—we shall be equally guilty of that betrayal."

Fervent Interpolation

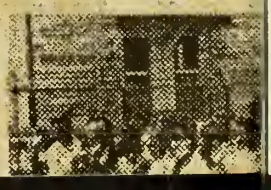
The President, speaking in the auditorium of the War Memorial Opera House, built in memory of sons of the Golden Gate city who gave their lives in the first World War, in which he himself served, seemed to give unconscious expression to the solemn feeling of the occasion when, at the outset of his speech, he interpolated the words, half a hope, half a prayer:

"Oh, what a great day this can be in history!"

Just before the plenary session

JOL SIGN the Draf Ends No

WASHINGTON, Jan. 27, 1973—"With the signing of the peace agreement in Paris today, and after receiving a report from the Secretary of the Armed



PATIENT PACKAGE INSERTS: A CONCEPT WHOSE TIME HAS COME?

The consumer's right to know is an irreversible and desirable trend of the Seventies. It extends, and properly, to a patient's right to know more about his or her prescription medications. One way, gaining favor, is through patient package inserts. Wisely-prepared and properly distributed when medically indicated, they could markedly improve patient knowledge and drug therapy—laudable goals by anyone's standards.

The PMA endorses these goals and will work with government, the health professions and consumers to achieve them.

The Advantages

The concept holds promise of benefits: better patient understanding of the product prescribed, better adherence to the treatment plan, and more awareness of possible side reactions.

Every doctor has had patients who fail to finish antibiotic regimens because they feel better. Some patients assume that if one tranquilizer or analgesic is good, two may be twice as good. Still others fail to report dizziness while on antihypertensive therapy —and so on.

Problems like these might arise less often if the patient received written information in addition to verbal instructions. Some studies suggest that patients are more receptive to such materials, and they more often understand the verbal instructions and follow them, when inserts are used.

The Disadvantages

There are also some potential problems. Obviously, the inserts must be clearly phrased, without extraneous or complex detail. How much information is enough? How can it be kept current? Should all patients receive the same information? Should inserts be included with all drugs? Should only potential problems be listed or are patients better off with a "fair balance" presentation that describes usefulness as well as drawbacks?

These and similar questions require answers, since model inserts have yet to be properly developed and tested. Despite the need for these studies, the FDA is proceeding prematurely with inserts on selected products. We think the Congress is the only place where the matter can be given the proper legal status and direction, particularly since it represents a conceptual change in the legal, medical and social framework of the nation's prescription drug information system.

The Solution

The PMA believes that carefully-devised pilot studies of various kinds of inserts are needed. They should be developed and implemented with full participation by doctors, pharmacists, consumers, communications experts and the drug industry. Such studies will provide reliable pathways to follow, so that inserts will be useful aids to medical practice.

And particularly we think that you should be closely involved in this debate and in these studies and decisions. Otherwise, people with less experience and qualifications may control the purposes, content and use of a tool with considerable promise for improved patient care. It could make a difference in your practice tomorrow, and more importantly, in the health of your patients.

PMA
THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION
1155 FIFTEENTH ST, N. W. WASHINGTON, D. C. 20005

(Continued from Page 36)

March 21—**Urology—Common Office Problems and Treatment.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Chr., Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

March 29-April 2—**Controversial Areas in Surgery—15th Annual Seminar.** UCLA at Canyon Hotel, Palm Springs. Wednesday-Sunday. 13 hrs. $195.

March 30-31—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs.

April 2-6—**Vascular Surgery—6th Annual Symposium.** UCLA at Canyon Hotel, Palm Springs. Sunday-Thursday.

April 7-8—**Intraocular Lens Implantation Course.** Santa Monica Hospital, Santa Monica. Friday-Saturday. $600; $300, residents and military. Contact: Intraocular Lens Implantation Course, SMH, 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

April 12-14—**Maxillofacial Trauma—Soft Tissues Reconstruction and Facial Nerve Injury.** UCSF. Wednesday-Friday.

April 13-15—**General Surgery—Annual Course.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday.

April 15-22—**Orthopedic Review.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

April 16-21—**California Society of Anesthesiologists — 2nd Hawaii Seminar.** Hyatt Regency Hotel, Waikiki-Honolulu. Sunday-Friday. 20 hrs. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

April 18—**Orthopaedics—Common Office Problems and Treatment.** Eskaton Colusa Healthcare Center, Colusa. Tuesday; 7:30-9:30 p.m. $20. Contact: Vincent C. Sansone, MD, Cont. Med. Ed., Eskaton Colusa Healthcare Ctr., 199 E. Webster St., Colusa 95932. (916) 458-5844.

April 20-21—**Current Concepts of Macular Structure, Function and Disease—9th Annual Jules Stein Lecture and Postgraduate Seminar.** Jules Stein Eye Institute and UCLA at Century Plaza Hotel, Los Angeles. Thursday-Friday. $225. Contact: Lu Hendricks, Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

April 29-May 6—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $275.

May 6—**Retinal Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $200. Contact: Lu Hendricks, Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

May 6-7—**American Society of Anesthesiologists Workshop.** St. Francis Hotel, San Francisco. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

May 11-12—**Office Orthopedics.** USC. Thursday-Friday.

May 18-20—**Neurosurgery.** UCSF at Sheraton Palace, San Francisco. Thursday-Saturday.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

January 14-15—**Practical Pulmonary Diseases for the Primary Care Physician.** See Medicine, January 14-15.

January 18-20—**Infectious Disease.** USC. Wednesday-Friday.

January 19-20—**Biofeedback Techniques in Physical Medicine and Rehabilitation.** Herrick Memorial Hospital, Berkeley. Thursday-Friday. Contact: Marie Ham, Med. Staff Sec., Herrick Mem. Hosp., 2001 Dwight Way, Berkeley 94704. (415) 845-0130, ext. 418.

January 19-20—**Longevity Research Institute—2nd Annual Meeting.** With LLU at Longevity Research Institute, Santa Barbara. Thursday-Friday. 10 hrs. Contact: Mr. Bob Palmer, LRI, 1121 E. Cabrillo Blvd., Santa Barbara 93103. (805) 966-3967.

January 19-21—**Medical Aspects of Aging.** UCLA at Sheraton Universal Hotel, Universal City. Thursday-Saturday.

January 21—**Systemic Disease/Eye, Mouth, Skin Manifestations.** Continuing Medical Education/San Luis Obispo Consortium at Hilton Inn, San Luis Obispo. Saturday. 5 hrs. $25 for non-consortium members. Contact: Billy Mounts, MD, Chr., CME/SLO Consortium, P.O. Box 319, San Luis Obispo 93406.

January 23-27—**Therapy: Principles and Use of Drugs.** STAN. Monday-Friday. 27 hrs. $265.

January 28-29—**Pediatrics for the Primary Physician: A Practical Update.** UCLA. Saturday-Sunday. 10 hrs. $135.

January 30-February 4—**Family Practice Refresher Course—9th Annual.** UCI at Newporter Inn, Newport Beach. Monday-Saturday.

February 2-3—**Family Planning, Human Sexuality and Venereal Disease.** DREW at Hyatt House, Long Beach. Thursday-Friday. 15 hrs.

February 3-5—**American Medical Association—Regional Program.** Sahara Tahoe Hotel, Stateline. Friday-Sunday. Contact: UCD or Mr. G. K. Jewett, Dir., Dept. of Cont. Ed. Seminars, AMA 535 N. Dearborn St., Chicago 60610. (312) 751-6000.

February 8-11—**Primary Care—Current Management of Common Office Problems.** UCSF at Golden Gate Holiday Inn, San Francisco. Wednesday-Saturday.

February 10-11—**Alcoholism Update—4th National Seminar.** Vista Hill Foundation at Hotel del Coronado, Coronado. Friday-Saturday. 9 hrs. Contact: Virginia Everett, Dir., Public Relations, Vista Hill Foundation, 7798 Starling Dr., San Diego 92123. (714) 278-6761.

February 10-12—**Headaches: Evaluation and Management.** UCLA at Beverly Hilton Hotel, Beverly Hills. Friday-Sunday. 18 hrs.

February 12-13—**Workshop on Alcoholism—A Clinical Approach for Health Professionals.** UCSD at Sheraton Inn-Airport, San Diego. Sunday-Monday. 13 hrs.

February 13-17—**LLU Alumni Association—Annual Postgraduate Convention.** LLU. Monday-Friday.

February 15-17—**Course for Physicians in Family Practice—27th Annual.** Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Ann Raisbeck, Dept. of Med. Ed., Mt. Zion Hospital and Med. Ctr., P. O. Box 7921, San Francisco 94120. (415) 567-6600, ext 2401.

February 15-19—**Edward Tyler Symposium on the Practical Management of the Infertile Couple.** Tyler Med. Clinic and Century City Hosp. at Hilton Hotel, Las Vegas. Wednesday-Sunday. Contact: Jaroslav J. Marik, MD, 921 Westwood Blvd., Los Angeles 90024.

February 16-17—**Selected Topics in Geriatric Medicine.** STAN and Palo Alto VA Hospital at Stanford. Thursday-Friday.

February 19-24—**Caring for Older Persons.** Medical Communications and Services Assn. at Kona Surf Hotel, Kailua, Kona, Hawaii. Sunday-Friday. 31 hrs. $195. Contact: MCSA, 315 University District Bldg., 1107 N. E. 45th St., Seattle, WA 98105. (206) 633-0505.

February 22-24—**Daily Decisions in Lung Diseases.** Calif. Thoracic Society at Balboa Bay Club, Newport Beach. Wednesday-Friday. $150, members; $175, nonmembers. Contact: Elma Plappert, Exec. Sec., CTS, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

February 25-26—**National Symposium on Aging.** UCSF. Saturday-Sunday.

February 26-March 3—**Clinical Management of Sexual Problems.** Medical Communications and Services Assn. at Sheraton Hotel, Molokai, Hawaii. Sunday-Friday. 30 hrs. $195. Contact: MCSA, 315 University District Bldg., 1107 N. E. 45th St., Seattle, WA 98105. (206) 633-0505.

February 27-March 3—**Basic Science for Clinicians.** STAN. Monday-Friday. 25½ hrs. $265.

March 4—**Controversies in Applied Immunotherapy.** UCSF at Children's Hospital, San Francisco. Saturday.

March 4-5—**Current Trends in the Management of Common Genetic Disorders.** UCLA. Saturday-Sunday.

March 6-8—**Diagnosis, Treatment and Prevention of Genetic Disease.** American College of Physicians; Harbor Gen. Hospital; Nat'l Foundation-March of Dimes at Riviera Hotel, Palm Springs. Monday-Wednesday. Contact: Registrar, ACP, 4200 Pine St., Philadelphia 19104.

March 7-May 23—**Bedside Clinics.** USC at Children's Hospital, Los Angeles. Tuesday evenings.

March 8-10—**Neurology for Non-Neurologists.** UCSD at Hilton Hotel, San Diego. Wednesday-Friday. 22 hrs.

March 10-12—**American Medical Association—Regional Seminar.** Newporter Inn, Newport Beach. Friday-Sunday. Contact: G. K. Jewett, Dir., Dept. of Cont. Ed. Seminars, AMA, 535 N. Dearborn St., Chicago 60610. (312) 751-6000.

March 11-12—**Liaison Psychiatry.** UCLA. Saturday-Sunday. 14 hrs.

March 14-18—**Sports Medicine for the Primary Physician.** Univ. of Hawaii School of Medicine at Princess Kaiulani Hotel, Honolulu. Tuesday-Saturday, 18 hrs. $200. Contact: Univ. of HI Sports Medicine Course, Hawaii Conference Services, P.O. Box 22670, Honolulu 96822.

March 15-18—**Critical Care Medicine.** USC at MGM Grand Hotel, Las Vegas. Wednesday-Saturday.

March 17-19—**Family Practice—Intensive Review.** DREW. Friday-Sunday.

March 17-22—**California Medical Association—107th Annual Session.** Fairmont Hotel, San Francisco. Friday-Wednesday. Contact: Linda Ramsey, CMA.

April 2-7—**Electrophysiology.** USC at Erawan Gardens, Palm Springs. Sunday-Friday.

April 8-9—**Stress: Medical Management.** UCLA at Palm Springs. Saturday-Sunday. 14 hrs.

April 12—**The Prostate.** LLU. Wednesday. 4 hrs. $25.

April 17-19—**Stress Workshop.** UCLA at Yosemite. Monday-Wednesday. 15 hrs.

April 22-23—**Practical Dermatology for the Primary Care Physician.** UCLA. Saturday-Sunday.

April 22-29—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

April 27-29—**San Joaquin Counties Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Thursday-Saturday. Contact: Richard Manley, CMA.

April 29-30—**Sports Medicine.** UCLA. Saturday-Sunday.

May 15-21—**Diving Medicine.** UCSF at VA Hospital, Fresno. One week.

May 21-26—**Orthopaedic Symposium for the Family Practitioner.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sunday-Friday.

Audio-Digest Foundation. A nonprofit educational subsidiary of the California Medical Association. Twice-a-month tape-recorded summaries of leading national meetings. Services by subscription in: Anesthesiology, Family Practice, Internal Medicine, Obstetrics/Gynecology, Ophthalmology, Otorhinolaryngology, Pediatrics, Psychiatry, Surgery. ($90.00 per year for 24 one-hour cassettes or reels.) New catalog of lectures and panel discussions in all areas of medical practice also available, as well as cassette album condensations of the following 1977 specialty meetings: postgraduate courses from the annual meeting of the American Psychiatric Assn., workshops from the annual meeting of the American College of Physicians, and postgraduate courses from the annual sessions of the American College of Obstetricians and Gynecologists. For further information on subscriptions, catalogs and special courses, contact Mr. Claron L. Oakley, Editor, 1577 E. Chevy Chase Dr., Glendale 91206.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Physician-in-Residence Preceptorship in Pulmonary Disease. USC, Pulmonary Disease Section, Dept. of Medicine and Postgraduate Medical Education. One month or more, by arrangement. Opportunity for practicing physician to achieve specified knowledge and skills in adult pulmonary medicine. Contact: Oscar J. Balchum, MD, PhD, USC.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Department of Internal Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen R. Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, 97201.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

INTERNAL MEDICINE

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

December 15—**Circuit Course Program on Lower GI.** St. Anthony Hospital, Pendleton. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Ave., Portland 97201.

December 15—**Current Concepts in Exercise Testing and Training in Coronary Heart Disease.** YMCA, Portland. Contact: M. R. Malinow, MD, 505 NW 185th Avenue, Beaverton 97005.

January 5—**Circuit Course Program on Stroke Prevention.** Recreation Cafe, The Dalles. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Ave., Portland 97201.

January 11—**Circuit Course Program on Endocrinology.** Douglas Community Hospital, Roseburg. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Ave., Portland 97201.

January 12—**Circuit Course Program on Endocrinology.** Thunderbird Courtel, Coos Bay. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Ave., Portland 97201.

January 18—**Circuit Course on Stroke Prevention.** Salem Memorial Hospital, Salem. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Ave., Portland 97201.

January 25—**Circuit Course on Stroke Prevention.** Rogue Valley Memorial Hospital, Medford. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Ave., Portland 97201.

January 26—**Circuit Course on Stroke Prevention.** Sacred Heart Hospital, Eugene. Contact: Joyce Gullixson, OMA Headquarters, 5210 SW Corbett Ave., Portland 97201.

WASHINGTON, ALASKA, MONTANA AND IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-64, Seattle, Washington 98195. Phone: (206) 543-6995.

December 14-16—**Leukemia, Lymphomas and Advances in Medical Oncology—Univ. of Wash. Internal Medicine Review Sessions in Montana.** Wednesday, Dec. 14, Great Falls. Contact: Mr. John Breeden, Box 2829, Great Falls, MT 59403. Thursday, Dec. 15, Billings. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, Dec. 16, Missoula. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

January 6-7—**Radiology of the Pancreas and Biliary Tract.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1110 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

January 18-20—**Problems in Clinical Endocrinology—American College of Physicians.** Wednesday-Friday. Virginia Mason Medical Center Auditorium, Seattle. Contact: American College of Physicians, 4200 Pine St., Philadelphia, PA 19104. (215) 243-1200.

January 23-24—**Coronary Artery Surgery—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, Jan. 23, Wenatchee. Contact: William M. McKee, MD, P. O. Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, Jan. 24, Yakima. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 248-6791.

January 25-27—**Coronary Artery Disease—Univ. of Wash. Internal Medicine Review Sessions in Montana.** Wednesday, Jan. 25, Great Falls. Contact: Mr. John Breeden, P.O. Box 2829, Great Falls, MT 59403. (406) 453-1493. Thursday, Jan. 26, Billings. Contact: Mrs. Frances Burt, Continuing Medical Education, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, Jan. 27, Missoula. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

January 26-28—**The Macula and Fluorescein Angiography—Washington State Academy of Ophthalmology President's Meeting.** Thursday-Saturday. Washington Plaza Hotel, Seattle. 15 hrs. Contact: Charles E. Boylan, MD, 1601 16th Ave., Seattle, WA 98122. (206) 325-8500.

February 3-4—**Pharmacology for the Practitioner.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle WA 98101. (206) 223-6898.

February 13-16—**Pediatric Gynecology—Univ. of Wash. Pediatrics Sessions in Idaho, Montana, Washington.** Monday, Feb. 13, Pocatello. Contact: Robert H. Judd, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443. Tuesday-Wednesday, Feb. 14-15, Spokane. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220. Wednesday-Thursday, Feb. 15-16, Great Falls. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

February 14-17—**Oncology.** Tuesday-Friday. 8-10 a.m., St. Joseph Hospital, Tacoma, Wash. Contact: College of Medical Education, University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

February 15—**Headaches—Univ. of Wash. General Medicine Sessions in Anacortes, Washington.** Contact: Harry Eiesland, MD, 24th and "M" Ave., Anacortes, WA 98221. (206) 293-3101.

February 22-24—**Immunoglobulins and Immunologic Disaster—Univ. of Wash. Internal Medicine Review Sessions in Montana.** Wednesday, Feb. 22, Great Falls. Contact: Mr. John Breeden, P.O. Box 2829, Great Falls, MT 59403. (406) 453-1493. Thursday, Feb. 23, Billings. Contact: Mrs. Frances Burt, Continuing Medical Education. Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, Feb. 24, Missoula. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

February 23-24—**Lower Intestinal Diseases—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, Feb. 23, Wenatchee. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, Feb. 24, Yakima. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 248-6791.

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